

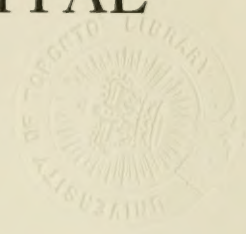
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THE

JOHNS HOPKINS HOSPITAL

BULLETIN



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CLINICAL OBSERVATIONS ON EPIDEMIC INFLUENZA¹

By ARTHUR BLOOMFIELD and GEORGE A. HARROP, JR.

(From the Medical Clinic of The Johns Hopkins Hospital)

During the recent epidemic of influenza, about 300 cases of the disease were admitted to The Johns Hopkins Hospital. Inasmuch as most of the patients were seen from the very onset of symptoms and went through their illness without complications, an unusual opportunity was afforded to study the clinical features of the entire course of the disease. The material was drawn from certain limited groups of individuals, to wit:

The nursing staff of the hospital (about 350 in number), living in the nurses' home.

The medical students (about 400 in number) quartered in boarding houses and clubs.

The hospital physicians (about 100 in number), residing mainly in the hospital.

The hospital service staff (about 200 in number), living mainly in the domestic home of the hospital or in the nurses' home.

Eight cases arose among the patients in the public wards and a few more were admitted as emergencies from various parts of the city.

Of the entire group, about 300, or approximately 30 per cent, developed the disease; of the nurses, nearly 40 per cent fell ill.

The main statistical facts of the epidemic are summarized in the following table and chart, which are based on the study of 268 patients admitted between September 24th and October 20th.

TABLE I

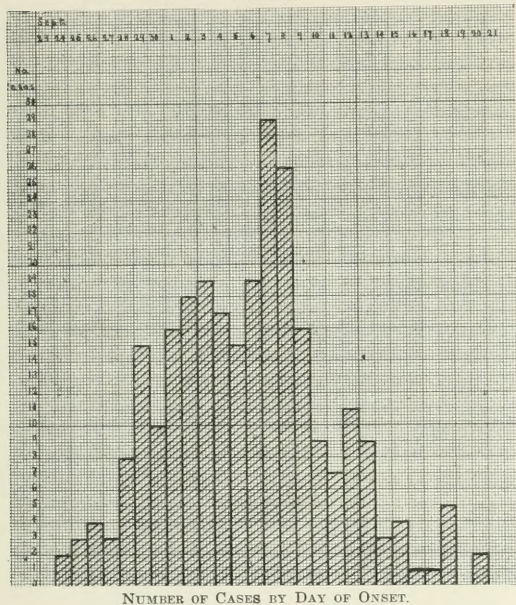
GENERAL STATISTICS OF THE INFLUENZA CASES IN THE JOHNS HOPKINS HOSPITAL

	No.	Per Cent
Total cases	268	
Total deaths	13	4.8
Total number developing pneumonia	41	15.3
Total deaths among pneumonia patients	13	32.0
Total deaths among patients in hospital from start of disease	7	2.7
Total number of patients in hospital from start of disease developing pneumonia	28	11.0
Total number of patients admitted with frank pneumonia	13	
Total deaths among patients admitted with pneumonia	6	46.0
Total deaths among patients developing pneumonia in the hospital	7	25.0
Total number of nurses admitted	123	
Total number developing pneumonia	12	9.8
Total deaths	3	2.4
Total deaths of patients developing pneumonia	3	25.0

¹Read before The Johns Hopkins Hospital Medical Society, November 18, 1918.

Chart I illustrates graphically the course of the epidemic. The rapid rise following the few preliminary cases, and the sudden drop after the height of the epidemic was reached, correspond with the curves of previous epidemics. With the sudden falling off in the number of cases there was a remarkable change in the clinical character of the disease. The fulminating type was no longer seen, the patients were much less ill, the erythema of skin and mucous membranes was slight or absent, pneumonia was much less frequent, and in general the picture approximated closely that seen in "influenza nostras," or "endemic grippe." All the patients who died fell ill before October 10th.

CHART I



The appearance of the epidemic made necessary a rapid reorganization of the hospital, in order to handle the increasing number of cases. This was made possible by the efficient activities of the superintendent's office and of the superintendent of nurses. The disposition of the patients was planned with the idea of preventing secondary epidemics of pneumonia. Not more than thirty patients were housed in one ward, the rows of beds were single, and screens were placed between every two beds. Each patient had a separate thermometer, and all linen, utensils and dishes were boiled after use. Paper towels, handkerchiefs and sputum cups were burned. The patients were instructed to cover the mouth when coughing, and all attendants wore gowns and gauze masks (4 to 8 thicknesses) while in the wards. As soon as pneumonia or any other complication developed, the patient was specially isolated in a separate room.

Each block of twenty to forty cases was in charge of an interne, assisted by one or more fourth-year medical students. They took the histories, made the notes, carried out the laboratory tests, and had charge of the immediate needs of the patients. The resident and assistant resident exercised systematic supervision over the wards, and the physician-in-chief consulted in the severe cases and advised generally in the conduct of the epidemic. Admission of patients was done by a set of externes rapidly trained in the diagnosis of influenza. Throughout the entire epidemic no case of another infectious disease was admitted to the influenza wards. The organization of the "influenza staff" would have been ideal had it not been necessary constantly to replace men stricken down by the disease. Thus, by the end of the epidemic the entire staff except three members had been renewed by successive substitutes.

It was found necessary to schematize in the handling of the patients, owing to the tremendous nursing problem. A set of routine orders for influenza cases was therefore worked out, which applied automatically to all patients. These orders covering the main needs of most patients were supplemented by any special directions necessary. Another routine was worked out for the regulation of the patients' activity during convalescence. This was found satisfactory in practically all the uncomplicated cases, and saved much labor for the ward staff. No medical or scientific books, or newspapers, were allowed in the wards. It was thought that the harrowing accounts of the epidemic in the latter might have a bad effect on patients already depressed.

The routine study of the case consisted of a history uniformly taken to cover in detail such questions as exposure and onset symptoms, a complete and thorough physical examination, a leucocyte count on admission, and at intervals until discharge, blood pressure on admission and discharge, urine examination on admission, repeated if abnormal findings were present, and two-hourly observations of temperature, pulse and respiration. Frequent detailed notes were made by the internes and staff on the course of the disease and its special features.

CLINICAL OBSERVATIONS

The material furnished an unusual opportunity to study the early stages of the disease, since about one-half of the cases were drawn from a closed group of individuals—namely, some 350 nurses residing in The Johns Hopkins Nurses' Home. At the start of the epidemic it was hoped that extensive spread among the nursing staff might be prevented by early detection and isolation. Communication between this group and the outside world was, therefore, almost completely cut off, and they came in contact only with each other, with the staff, and with the patients in the wards. Furthermore, they were instructed to report for observation at the first symptom of any sort. Practically all the cases, therefore, were seen from the very start, and it was possible to study in detail the earliest symptoms and the mode of onset. From these ob-

servations, it was clearly apparent that the disease is not primarily a local respiratory infection, and that it presents a clean-cut, definite clinical picture, quite independent of pulmonary complications. It should also be emphasized that influenza, as seen now, corresponds in detail with the descriptions of the previous pandemics—it is undoubtedly the same disease.

The disease is ushered in by two groups of symptoms; in the first place the constitutional reactions of an acute febrile disease—headache, general aching, chills, fever, malaise, prostration, anorexia, nausea or vomiting; and in the second place, symptoms referable to an intense congestion of the mucous membranes of the nose, pharynx, larynx, trachea, the upper respiratory tract in general, and of the conjunctiva. Superficially, the onset seems to vary in different cases, depending on whether one or the other of these sets of symptoms predominates, but a striking essential similarity prevails, which is most obvious during the height of the epidemic, when the disease runs more constantly true to type. For this reason it seems misleading to divide the ordinary run of cases into respiratory, abdominal and nervous. It would seem better to reserve the last term for those patients showing organic lesions of the nervous system or psychoses more outspoken than the usual temporary depressions.

Three distinct types of invasion were noted—abrupt invasion, gradual invasion and invasion with intermittent symptoms. The departure from health was extremely sudden in many of the cases, especially the severe ones at the height of the epidemic, definite symptoms beginning after only a few hours of vague malaise. In some cases the patient was knocked flat, literally dropping in his tracks. The most common symptoms were sudden and marked malaise and prostration, chills or chilly sensations, intense headache and general aching, pain in the eyes and photophobia. In a few instances, acute abdominal pain, vomiting or diarrhea ushered in the disease. In these severe cases the temperature usually rises rapidly, reaching its height within 24 hours. Coincident with, or shortly following onset, as the hyperemia of the mucous membranes develops, there is dryness, tightness, fullness, or slight rawness of the throat, substernal discomfort, and tight, racking cough, without sputum. There may be stoppage of the nose from swelling of the mucous membrane, with slight watery nasal discharge, and conjunctivitis is practically always present. The remarkable flushed appearance of the face and buccal cavity to be described below is usually fully developed in twenty-four hours. In another large group of cases the invasion is gradual, the symptoms unfolding themselves over a period of one to three days before the disease becomes full blown. It is in this group that isolated symptoms, such as headache, sore eyes, "coryza," raw throat, dry cough, anorexia, insomnia, or pain in the back may for a time predominate, masking at first the essential identity of all the cases. During such a period of invasion the temperature is usually normal, or only slightly elevated. In the early part of the epidemic, we observed many cases of this sort for two or three days, uncertain as to the diagnosis,

until sudden high fever and frank symptoms and signs made the condition obvious. In a third group of cases the early symptoms were very puzzling, because of their intermittent nature. Thus, headache and malaise might be present one day and gone the next. Nausea might then come on for a few hours, again leaving the patient feeling well. After alternating periods of minor symptoms and well-being, lasting for several days, the full-blown disease finally made its appearance.

Of particular interest were certain symptoms that were present within the two weeks preceding the onset, but which apparently were independent of the actual disease. Such phenomena were noted in 36 instances; for example, S. had headache and a cold for two weeks, and H. had slight cough and occasional malaise for five days before onset. M. had coryza which cleared up two days before onset, K. had sore eyes and photophobia for a week, and N. had "coryza earlier in the week, which had practically subsided at onset." C. had been nervous and restless for four days, and J. had had a cough for two weeks before onset. In general, these "pre-onset" symptoms were in the nature of mild upper respiratory tract disturbances of from one to two weeks' duration, usually improving or well at the time of definite onset of the influenza.

Physical Examination.—Although evidence of gross lesions is absent in uncomplicated cases, the physical findings are none the less clean-cut and typical. The general appearance is most striking. In well-marked cases, there is an intense, dusky, reddish-plum-colored erythema of the face, lips and upper chest, which usually fades off abruptly at the level of the breast, but may extend over the entire chest and back, and occasionally involves the arms and legs. The entire facies has a remarkable suffused look, not unlike that seen in polycythemia vera. It is, however, quite different from true cyanosis, and studies of the oxygen-combining capacity and content of the blood in these patients gave normal results. The color blots out on pressure, returning instantly. In milder cases this tint is at times less striking, but it was present to some degree in practically all, and even where not obvious, a faint purplish erythema could be demonstrated by pressure. The peculiar dusky appearance of the face often persisted for weeks into convalescence, quite independent of transient flushing on exertion, which accentuated the underlying hue. In seven cases a fine, branny desquamation was noted over face and upper chest. Conjunctivitis was often very marked, with lachrymation and photophobia.

Early in the course of the epidemic we noticed an unusual bright red appearance of the throat in most of the patients, and more careful study of subsequent cases showed this to have striking and constant features. The changes in the mouth usually become full-blown during the first twenty-four hours of the disease. The most striking feature is a bright vermilion or scarlet injection of the pharynx, tonsils, pillars and soft palate. In many cases, this erythema extends over the entire mouth, and can be exquisitely demonstrated by pressure on the mucosa of the cheek with a spatula. In the

most marked cases, the entire mouth cavity has a flaming appearance. On analysis, this redness is seen to be due to a diffuse hyperemia of the mucous membrane, together with an injection of minute blood vessels on the pharynx and pillars, but especially on the soft palate. There is a line of demarcation at the hard palate, which is relatively free. In some cases, especially the mild ones, these changes are less marked, being confined to the soft palate and pillars. There is extreme swelling of the lymphoid tissue of the posterior pharyngeal wall, which gives it a remarkable corrugated appearance. These changes are clearly in the nature of an erythema, and there is never any localized exudate (Fig. 1).

The tongue is usually coated, but if clean is bright red like the buccal mucosa.

In from one-half to two-thirds of the cases at onset, one to three or four, or even more, dark, crimson spots were seen on the mucosa of the inside of the cheek (Fig. 2). They were occasionally present on the gums, soft palate, mucous border of the lips, or on the uvula. These spots vary from a minute pin-point up to one millimeter in diameter, and may be arranged in one or more clusters. The dark cherry color and sharp margin characterize them and seem to indicate that they are of hemorrhagic origin. The individual spots fade rapidly, disappearing without trace in from one to two days. They may reappear in repeated crops in the same individual, and are seen in convalescence in most of the cases. About 94 per cent of our patients in whom they were systematically looked for showed them at some time during the course of the disease.

Inasmuch as we had never observed such spots before, and were unable to find any account of them in the literature, it appeared at first as if they might be specific of influenza as Koplik's spots are specific of measles. After the epidemic, however, it was possible to examine several hundred mouths of individuals who had had no symptoms of influenza, and in them also these spots were frequently present. In 303 examinations of 55 controls made daily over a period of one to nine days, the spots were seen 110 times, or in 36.6 per cent. They were seen at some time in 84.2 per cent of 33 controls examined daily over a period of a week or more. It was striking, however, that the spots were usually much smaller and less bright than in the influenza patients. Although they are obvious and often picturesque in the latter, they are frequently so insignificant in the controls that they are found only on careful search. Possibly the hyperemia of the mouth in influenza presents a specially favorable condition for their development. Their exact cause is uncertain; they may be due to slight trauma to the mucosa of the mouth. So that although these spots are not a specific lesion, their presence in typical form may have a certain degree of clinical specificity.

Another striking feature in the appearance of the mouth was a swelling of the minute nodules normally present on the soft palate. They were often extremely prominent, appearing as white or gray glistening, rounded bodies, varying in

size from 1 to 3 millimeters in diameter. They were usually abundant, the entire soft palate being thickly seeded with them, and they stood out sharply against the surrounding hyperemia.

In summary, then, the mouth presents a very striking picture, which seems distinctly characteristic. Although, most writers have noted that the throat is injected, the observation by Tigri,² in 1867, now lost in obscurity, is the only one we have found which describes a typical enanthem. Tigri noted the peculiar injection of the soft palate, and likened it to the enanthem of measles.

The general appearance of the mouth may remain full-blown for about a week. The erythema then fades, usually leaving a striking capillary injection of the soft palate and pillars. In some cases, the redness of the entire mouth persisted for several weeks into convalescence.

Herpes was noted in nine per cent of the cases. In a few, it was present at onset, but might appear at any time during the active stage of the disease. It was no more frequent in the pneumonias than in the uncomplicated cases. There are no striking cardiovascular features; the pulse is usually only slightly accelerated, and the blood pressure tends to be sub-normal. Abdominal examination is essentially negative. The spleen was felt in only three cases. Unless complication sets in, the lungs are clear, although a few transient crackles could at times be heard over the lower lobes at the beginning of the examination. Minor skin rashes were noted in 10 cases. A few erythematous papules on the chest and shoulders or a few small petechiae were seen. Three patients had transient urticarial eruptions, and one a generalized morbilliform rash. In general, apart from the erythema, the skin changes are insignificant.

Course of the Disease.—Once fully established, the disease picture was remarkably constant. The fever usually continued high for from three to eight or nine days, with morning drops, the constitutional symptoms persisting until the temperature began to fall. At this time, particular discomfort, such as headache, backache, nausea, etc., gradually or suddenly disappeared, giving place to a profound feeling of collapse or exhaustion. The tight, racking cough often increased after the first day, with the production of more or less whitish, yellowish or greenish mucoid sputum, which in some cases persisted for weeks into convalescence. This is a regular feature of the disease, but other respiratory tract involvements must be regarded as complications. Some of the cases ran their whole course without cough, sputum or respiratory symptoms. Epistaxis was noted in 10 per cent of the patients. It occurred at onset, or at any time during the active stage, and in a few cases there were repeated epistaxes. This bleeding is doubtless associated with the hyperemic condition of the nasal mucosa. Nearly all the more severe cases had marked anorexia or nausea. The feeding problem became very difficult, and even fluid was

² Tigri: *Omodei annali di medicina*, Milan, 1867, CCII, 677.

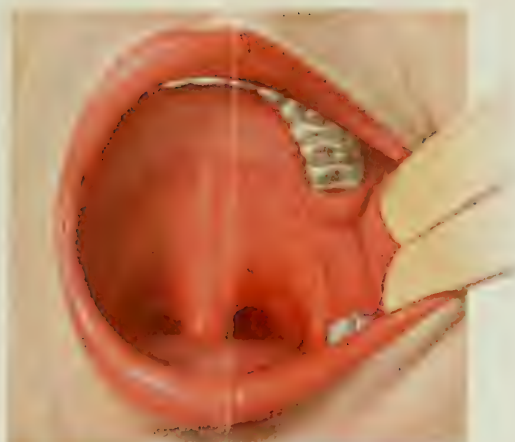
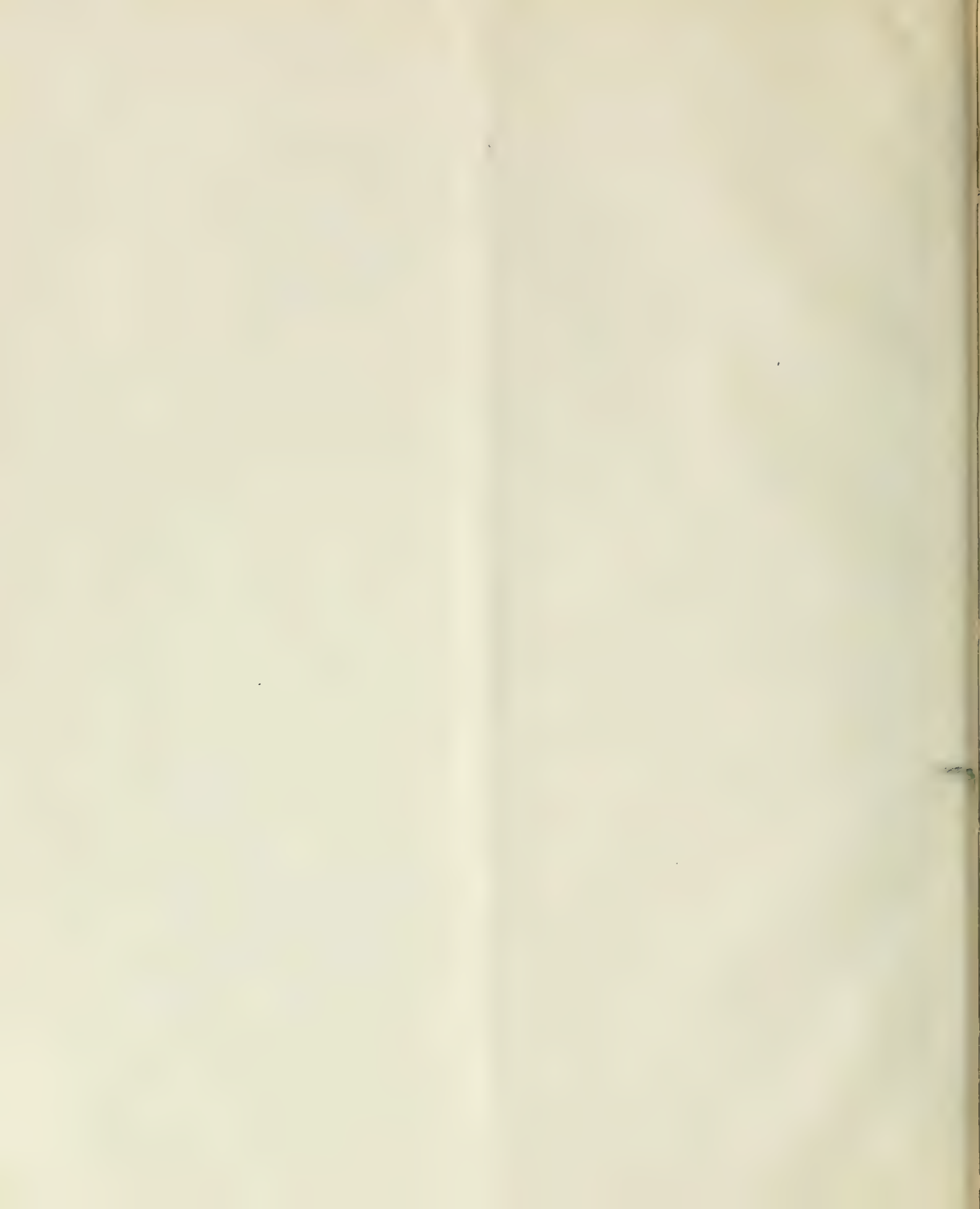


FIG. 1



FIG. 2



refused. Stubborn constipation was the rule, although a few patients had brief attacks of diarrhea. In no other disease does one see such constant lack of cheer in the patients' faces. Nothing satisfies them, they are extremely unhappy and gloomy, and seem to feel that things can never be normal or comfortable again. Pathological depressions were, however, strikingly absent in our cases.

Convalescence.—The classical post-influenzal asthenia described in previous epidemics was noted in these cases. Profound prostration persisted for weeks into convalescence. The patients for the most part feel fairly comfortable while lying flat in bed, but the slightest exertion is followed without warning by exhaustion, a feeling of collapse, sweating and palpitation. Apart from actual physical weakness, which is marked, they complain of an intensely disagreeable sensation, which may be best characterized as an extreme lack of well-being, rather than any positive pain or discomfort. This state of affairs usually persisted as long as the patients were under observation—about three or four weeks. Physical examination during convalescence is essentially negative. Tachycardia and sinus arrhythmias or extrasystoles are common, and in many cases the racking cough, with more or less mucoid or mucopurulent sputum persists. Anorexia, headache and insomnia were frequent complaints and loss of weight up to 20 pounds was not uncommon.

Mild, Abortive and Atypical Cases.—These were of particular interest from an epidemiological and diagnostic standpoint. During the course of the epidemic about 20 cases were observed with such slight symptoms and signs that the presence of any definite disease was doubted. It was only at the end of about a week, when typical prostration appeared, that the diagnosis was made certain. Many patients did not apply for medical aid until this period of the disease, presenting as cases of tachycardia, insomnia or general breakdown. They furnished the key to a still larger group of very mild or abortive cases, which indicate clearly that the total number of individuals affected is much greater than the number of manifest cases. In some of these individuals with practically no symptoms, the diagnosis was clinched by the typical appearance of the throat or by an extreme leucopenia.

Of the patients admitted to the wards, 30 ran an afebrile course, although there was usually some abnormality of the temperature curve. These were by no means the mildest cases; on the contrary, many who came down with sharp reactions recovered more promptly and were less prostrated.

LABORATORY EXAMINATIONS

Urine.—In the severer cases, a febrile albuminuria was present, usually clearing up promptly after free intake of water. No permanent renal disturbance was noted. The patients with pneumonia showed large amounts of albumin and casts.

Blood Pressure.—The blood pressure was either normal or low. Low readings were especially frequent in the very

asthenic cases. Systolic pressures of 80 to 100 mm. Hg., and diastolic pressures as low as 50 were common. In convalescence, the pressures were essentially normal.

Leucocytes.—Leucopenia was the rule during the active stage of the disease. The average counts on the first or second day were about 4000 to 5000, but they varied from 2000 up to normal numbers in different cases. The low count persisted into convalescence, usually returning to normal during the third or fourth week. In some cases the normal mark was overshoot, the count rising to 12,000 to 15,000—occasionally even higher. Differential counts during the stage of leucopenia usually show an absolute decrease of polymorphonuclears, with relative lymphocytosis. In some cases, the lymphocytes were absolutely decreased as well. It was of interest that many mild cases had extremely low counts, and that the leucocyte curves seemed unaltered by the occurrence of complicating bronchopneumonia.

TEMPERATURE CURVES

Temperature readings were taken every two hours throughout the acute stage. In Table II is summarized the day of

TABLE II

THE DURATION OF THE FEVER ACCORDING TO THE DAY OF DEFERVESCENCE, AND THE NUMBER OF CASES

Temperature became normal on—

Day of Disease	in	Number of Cases
1	0
2	0
3	7
4	15
5	25
6	24
7	44
8	28
9	22
10	6
11	4
12	1
		176

* Bronchopneumonia?

In 30 cases there was no fever during the hospital stay.

the disease on which the temperature became normal. It is apparent that this is not a three-day fever. Even in uncomplicated cases, the pyrexia usually lasts from five to nine days. From a study of complete temperature curves obtained in cases developing in the wards, it was possible to determine the details of the entire course of the fever. The following general statements may be made:

1. The temperature rises gradually at onset, rarely reaching its height in less than 24 hours.

2. Fever continues for a variable period, falling gradually in about one-half the cases, and suddenly (in 24-36 hours) in the remainder.

3. There is rarely a steady fastigium, the morning temperature usually being from one to three degrees lower than the evening reading.

4. After falling, the temperature may remain normal, it may be subnormal for several days, or there may be slight post-febrile rises.

5. Secondary rise of fever usually indicates a complication, but such rise may occur in uncomplicated cases.

6. An occasional chart may show an entirely bizarre, non-uniform curve.

7. Some charts show only slight elevations throughout the course.

8. The pulse is usually relatively slow, but follows the temperature curve in a general way.

It appears, therefore, that while the temperature curves vary in character, the fever is one of distinctly determinate duration. In 95 per cent of the cases the temperature reached normal by the ninth day, and in no uncomplicated case did it persist beyond the eleventh day. Some of the main features of the fever are shown in the appended charts.

COMPLICATIONS

Apart from the pneumonias, which occurred in 41, or 15.3 per cent of the cases, complications were few. Mild sinus infections occurred in two cases, catarrhal otitis media in six, while one patient developed an acute mastoiditis requiring operation. Laryngitis giving frank symptoms occurred three times.

A group of 19 patients was of particular interest. They developed localized patches of fine, crackling rales, with some impurity of breath sounds over one or both lobes. These signs usually appeared at the height of the disease and persisted for a few days to several weeks. A beginning pneumonia was naturally suspected, but in no case was there bloody sputum, respiratory symptoms, or any unusual rise of temperature. The normal course of the disease seemed unaltered. X-rays made in several of these cases showed no localized shadow.

EPIDEMIOLOGICAL OBSERVATIONS

Despite the striking general facts in regard to the gross spread of the disease, the details of contagion and infection are quite obscure. We desire to put on record certain observations which seem of interest, without attempting to draw any definite conclusions.

The disease is contagious during the incubation period. E. visited his sister who was at a country place where no influenza had appeared. He was there for a few hours in the morning. On his arrival in Baltimore six hours later, symptoms appeared. He had a severe type of the disease, with secondary pneumonia of which he died on the eighth day. Two days after contact the sister developed a severe case of influenza. Family H. were in the country with no influenza in the vicinity. Mrs. X. and her son came to visit them. A day or so later, the boy developed the disease. H., who is a physician, sent mother and boy away at the onset of symptoms, but three days later his own three children developed severe attacks. These observations are also in harmony

with the generally accepted idea that the incubation period is about two days.

Medical student B. came to Baltimore with the disease full-blown. His room-mate slept in the same bed with him for two nights, but did not develop influenza. Most of the nurses are quartered two in a room. Among 150 of them who developed influenza, there were only 12 pairs of room-mates. Except in the case of three pairs, each of the two came down within two days of the other. This perhaps indicates that infection took place mainly before symptoms were well developed, when the nurses were in general contact in the assembly rooms and dining hall. General use of gauze face masks in the wards did not seem to alter the course of the epidemic. If these masks are protective, infection from early unisolated cases must be assumed.

Only eight of the patients in the general public wards developed influenza, although 40 per cent of the attendants were affected; and numerous individuals did not contract influenza until they had been constantly exposed for as long as two weeks.

These observations are of interest in so far as they confirm facts noted in previous epidemics, and indicate our total lack of insight into the details of the mode of infection and spread of the disease, apart from the gross fact of its extreme contagiousness.

ETIOLOGY

A consideration of the etiology of influenza must include a discussion of two questions. Is the influenza bacillus the cause of the disease, and if not, what is the etiological agent? The main evidence in favor of the Pfeiffer bacillus' being the cause of influenza is the observation that in certain localities it has been isolated from the respiratory passages in a large percentage of the cases. Against its etiological nature, several facts may be noted: Apart from the presence of the organism, no definite relation to the uncomplicated disease by isolation from a specific lesion, or development of immunity reaction, has been proved. Neither experimentally in animal or in man has influenza or a condition simulating it been produced by inoculation with cultures of the influenza bacillus. The influenza bacillus is present in interepidemic times in the nasopharynx of normal persons, and in a large percentage of acute and chronic respiratory infections. Luetscher, for example, in 603 sputum cultures, isolated the influenza bacillus in pure culture from 28.5 per cent of cases of non-tuberculous infection. The organism is essentially symbiotic with other bacteria, both *in vivo* and *in vitro*. It is well known that it grows much better in the presence of other bacteria, such as staphylococci, giving rise to so-called giant colonies. In isolating pneumococcus from sputum by mouse inoculation, the influenza bacillus commonly comes through into the animal's blood with the pneumococcus, while other organisms remain localized in the peritoneum. Sputum cultures from cases of lobar pneumonia may yield *B. influenza* in pure or almost pure culture, where the lung puncture shows only pneumococcus, indicating the tendency

of the organism to press in wherever other bacteria are present. The influenza bacillus has been found in tonsils, inflamed and normal, in pleurisy, in sinus and middle ear infections, in the entire respiratory tract from nose to alveoli, in bronchiectases, in the urinary tract, in the meninges, and in association with tuberculosis, diphtheria, measles and scarlet fever. In these conditions, the rôle of the influenza bacillus, while superficially prominent, is clearly not fundamental.

Bacteriological studies, made in our cases by Dr. Howard, which are reported in detail elsewhere, did not bring evidence that the bacillus of Pfeiffer is the cause of epidemic influenza. Blood cultures made at onset in the acute cases were uniformly negative, and it was only in the terminal stage of the complicating pneumonias that organisms appeared in the blood. Pneumococcus or streptococcus was isolated in a few instances, but no influenza bacilli. Naso-pharyngeal swabs made at onset showed the usual mouth flora. Gram-negative bacilli were seen in smears in some of the cases, but only once as the predominating organism. In three instances of post-influenzal pneumonia, the Pfeiffer bacillus predominated in the sputum culture, but in most cases the pneumococcus, green streptococcus and other organisms were mainly present.

Similar bacteriological findings which are now being reported by other observers cast doubt on the rôle of the Pfeiffer bacillus as the primary cause of uncomplicated epidemic influenza; it is probable that the actual virus is as yet unidentified. It is of interest, however, to point out some

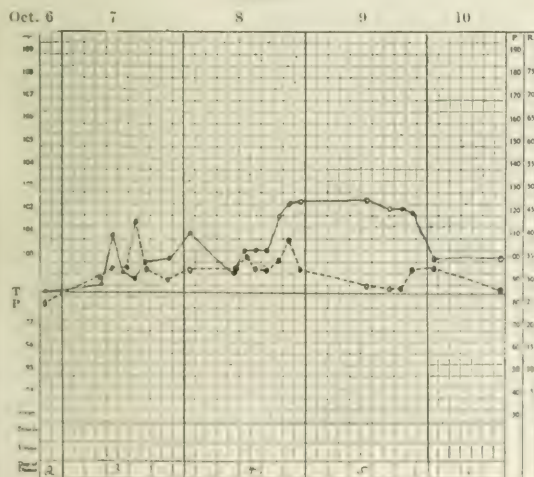
striking analogies between this disease and certain of the acute exanthemata, especially measles. They are both extremely contagious. They both tend to break out in epidemic form from time to time, but sporadic cases persist between epidemics. Each has an incubation period of strikingly constant length and a febrile reaction of determinate duration. They both have characteristic leucocytic changes. The uncomplicated cases all show striking absence of gross lesions. In both diseases there are hyperemic phenomena of the skin and throat, and a remarkable tendency to complications, especially in the respiratory tract. It should, however, be strongly emphasized that there is no evidence of any actual relationship between these two diseases.

CONCLUSIONS

The observations herewith presented may be summarized as follows:

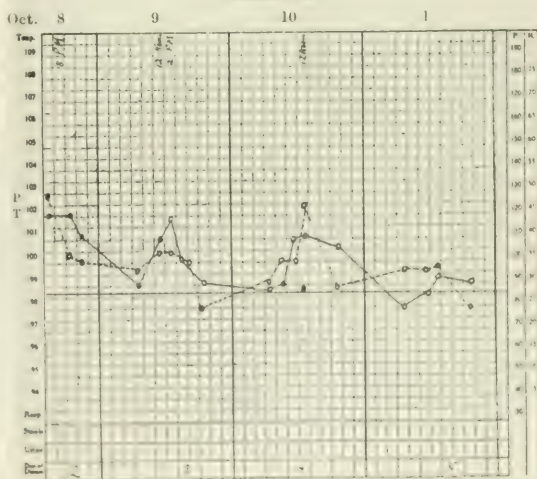
1. Epidemic influenza in 1918 is clinically identical with the disease as seen in previous pandemics.
2. It is not primarily a local disease of the respiratory tract.
3. It presents a definite and characteristic clinical picture quite apart from the pulmonary complications.
4. The main features of the uncomplicated disease are a constant set of symptoms, characteristic erythema and appearance of the mouth, fever of determinate duration, and leucopenia.
5. Proof is lacking that the Pfeiffer bacillus is the primary cause of uncomplicated influenza.

CHART II



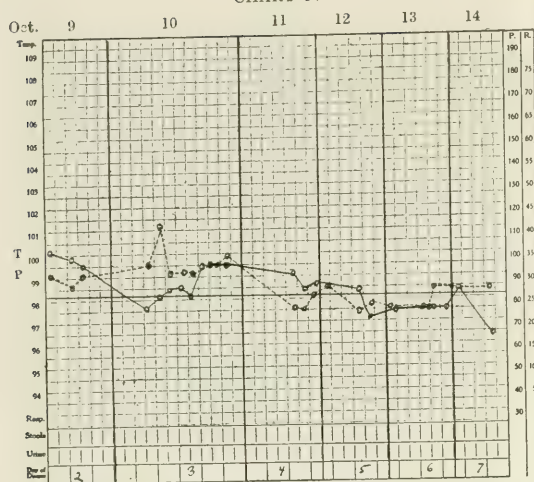
MODERATELY SEVERE CASE—UNCOMPLICATED. SHOWS GRADUAL RISE OF FEVER OVER 4 DAYS BEFORE HIGH POINT WAS REACHED.

CHART III



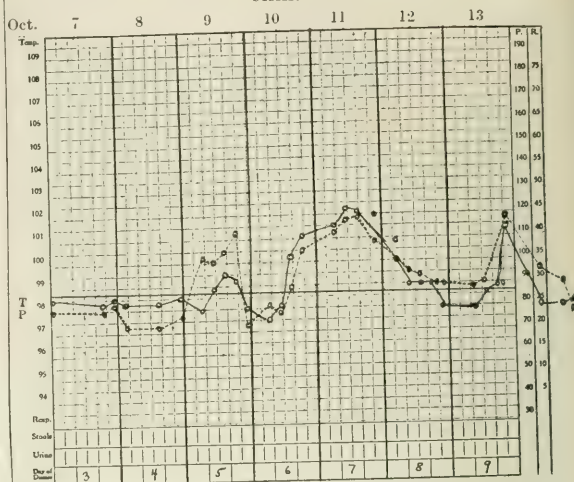
RAATHER SEVERE CASE—UNCOMPLICATED. SHOWS INTERMITTENT TYPE OF FEVER WITH CORRESPONDING PULSE.

CHART IV



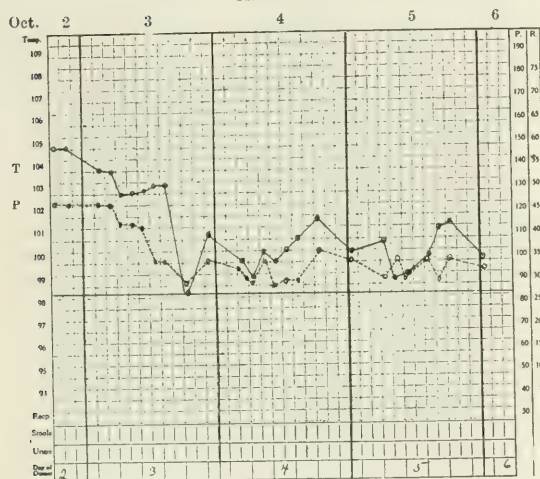
AN EXTREMELY SEVERE CASE. CHART SHOWING ONLY SLIGHT FEVER.

CHART V



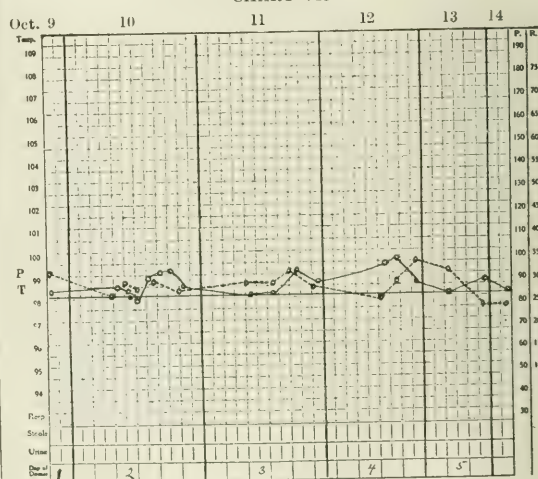
MODERATELY SEVERE CASE—UNCOMPLICATED. SHOWS LATE RISE OF TEMPERATURE ON THE 6TH TO 8TH DAY.

CHART VI



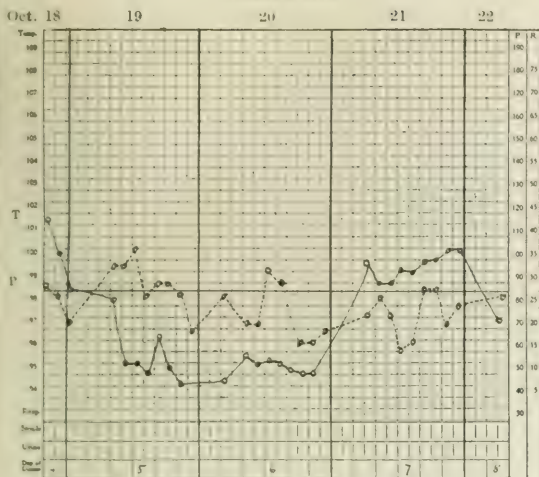
A FULMINANT CASE. CHART SHOWS VERY HIGH FEVER.

CHART VII



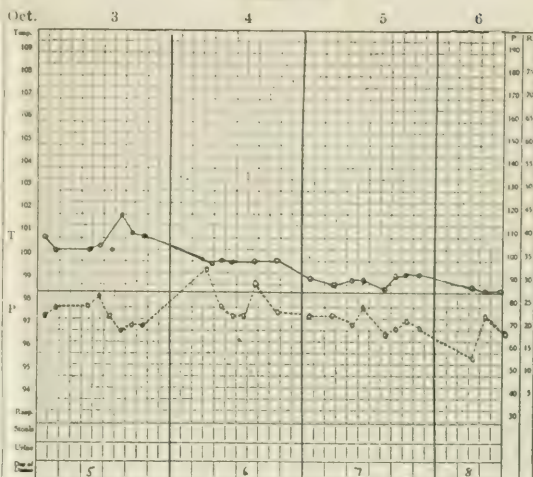
MODERATELY SEVERE CASE SHOWING VERY SLIGHT FEVER.

CHART VIII



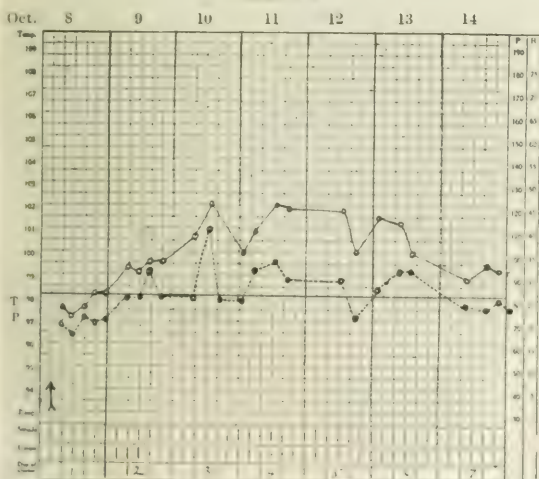
MODERATELY SEVERE CASE—UNCOMPLICATED. SHOWS FEVER FOLLOWED BY SUBNORMAL TEMPERATURE.

CHART IX



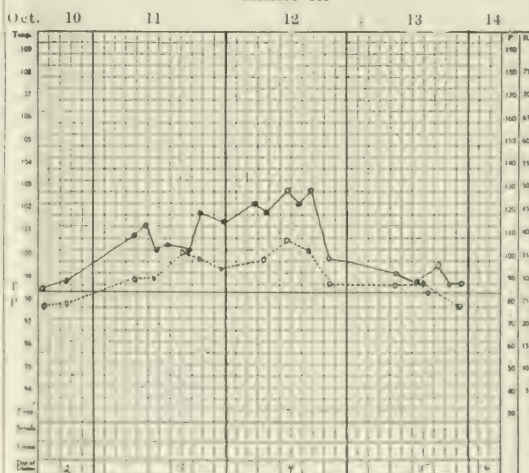
VERY SEVERE CASE—UNCOMPLICATED. SHOWS CHART FROM 5TH-8TH DAY. GRADUAL FALL OF TEMPERATURE—RELATIVE BRADYCARDIA—ABSOLUTE BRADYCARDIA IN CONVALESCENCE.

CHART X



A PATIENT WHO CONTRACTED INFLUENZA IN THE WARD. SYMPTOMS BEGAN AT 8 A.M. SHOWS GRADUAL RISE OF TEMPERATURE.

CHART XI



A FULMINATING CASE WITH INTENSE SYMPTOMS ESPECIALLY HEADACHE. CHART SHOWS GRADUAL RISE OF FEVER. SUDDEN FALL OF FEVER WITH PROMPT RELIEF OF SYMPTOMS ON 5TH DAY—FOLLOWED BY PROSTRATION.

THE BEHAVIOR OF THE BLOOD TOWARD OXYGEN IN INFLUENZAL INFECTIONS

By GEORGE A. HARROP, JR.

(From the Medical Clinic of The Johns Hopkins Hospital)

The general clinical picture in the cases of bronchopneumonia occurring during the recent epidemic of influenza is too well known to need detailed restating. Outstanding features, which bear on the present discussion, are as follows: frequently an insidious onset towards the end of the acute influenza; cyanosis, often blended with the intense, dusky erythema of the uncomplicated influenza; absence during the early part of the attack of any marked respiratory distress; and, until the moment of collapse, good circulation. The pulse is often but little accelerated, and is nearly always of good quality. In most of the fatal cases, during a period of from 24 to 36 hours before death, the patient's condition is profoundly changed. The respirations are accelerated, the pulse becomes rapid and weak, and a most striking cyanosis rapidly develops. The patient may become unconscious, but frequently remains perfectly alert and apprehensive almost to the moment of death. The peculiar color of these patients suggested an examination of the oxygen content of the blood.

The oxygen content of the blood in lobar pneumonia has been studied by Peabody,¹ who found in most uncomplicated cases that the decrease of respiratory surface due to the consolidation is completely compensated for; that is, there is no demonstrable disturbance of the respiratory exchange, and the oxygen content of the blood is within normal limits. His estimations were made by the method of Barcroft and Haldane,² as modified by Brodie.³ The oxygen content of the peripheral venous blood in his control cases varied between 9.23 and 15.02 volumes per cent. He found no definite relation between either temperature or respiration and the oxygen content of the blood. In a number of fatal cases of lobar pneumonia, where the termination was gradual, the patient becoming slowly weaker and more toxic, cyanosis increasing and pulmonary edema coming on, he found a progressive decrease in the oxygen content of the blood. In such instances, specimens taken at about the time of death showed a low oxygen-combining power. The fall in the latter was less marked than the fall in the actual oxygen content of the venous blood, although the two were roughly parallel. The lowest value for the oxygen-combining power at death he found to be 7.87 per cent. All of his other cases gave values above 13 per cent. He found similar phenomena in the blood of rabbits with a severe pneumococcal bacteremia.⁴ In experiments in which the pneumococcus was grown in a mixture containing unclaked red blood cells or

hemoglobin, he showed, in collaboration with Butterfield, that methemoglobin is formed and may be demonstrated by spectroscopic methods. It is probably this alteration of the hemoglobin which lowers the power of the blood to take up oxygen.⁵

A fairly simple technique for estimating the oxygen content of the peripheral venous blood has been devised recently by Lundsgaard.⁶ In determinations on 12 normal persons, he found that the oxygen content of the peripheral venous blood averaged about 13.50 volumes per cent, or about two-thirds that of the total oxygen capacity of the blood, which is variously stated. It is probably about 22 volumes per cent for the average normal individual.⁷ He stresses the important point that the oxygen content of the venous blood is difficult to interpret, unless a simultaneous determination is made of the total oxygen-combining power of the hemoglobin. The difference between these two values he terms the *oxygen unsaturation* of the blood, since it is a measure of that part of the hemoglobin whose oxygen-combining power is not fully saturated. The oxygen unsaturation of the venous blood in his normal controls, as well as in cases with compensated circulatory disturbances with regular pulse, varied between 9 and 2.5 volumes per cent, the average being about 5.8 volumes per cent. There are very few clinical reports dealing with determinations of venous oxygen tension. Obvious difficulties have so far rendered estimations upon the arterial blood impracticable. They can be safely made, however,⁸ and we shall report shortly our observations on the oxygen content of the arterial blood in a number of pulmonary and cardiac diseases.

The determinations included in this report have been made upon nine cases of post-influenzal bronchopneumonia, three of them fatal, and upon four uncomplicated cases of influenza, in the early hyperacute stage, when the characteristic dusky erythema or "cyanosis," was most striking. The oxygen content of the venous blood was determined by Lundsgaard's method. A pipette filled with oxalate crystals was attached to a bit of rubber tubing and thence to the needle. After withdrawal, the blood was immediately transferred to a tube under a layer of oil, to prevent contact with the air. It was found that a glass syringe with a snugly-fitting greased plunger can be employed with equal facility,⁹ the middle

¹ Butterfield, E. E., and Peabody, F. W.: Jour. Exp. Med., 1913, XVII, 587.

² Lundsgaard, C.: Jour. Biol. Chem., 1918, XXXIII, 133.

³ Palmer, W. W.: Jour. Biol. Chem., 1918, XXXIII, 119.

⁴ Hürter: Deutsch. Arch. klin. Med., 1912, CVIII, 1.

⁵ Means, J. H., and Newburgh, L. H.: Trans. Assn. Am. Phys., 1915, XXX, 58.

¹ Peabody, F. W.: Jour. Exp. Med., 1913, XVIII, 7.

² Barcroft, J., and Haldane, J. S.: Jour. Physiol., 1902, XXVIII, 322.

³ Brodie, T. G.: Jour. Physiol., 1909-10, XXXIX, 391.

⁴ Peabody, F. W.: Jour. Exp. Med., 1913, XVIII, 1.

portion of the blood withdrawn being used for the oxygen content estimations and the remainder for determinations of the total oxygen capacity, which were done by the method of Van Slyke.¹⁰ From the latter, the percentage of hemoglobin was calculated according to the commonly used standard of

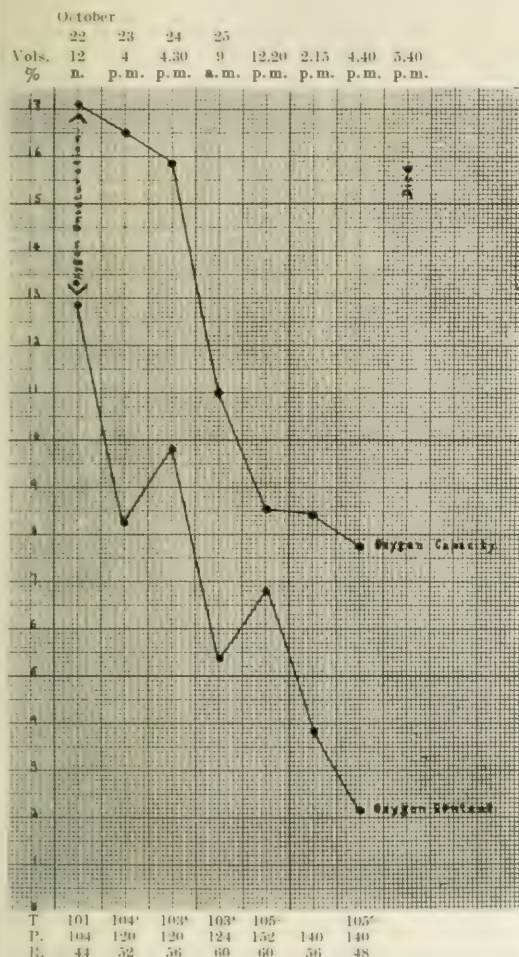


CHART 1.—The Oxygen Capacity and Content of the Peripheral Venous Blood of a Fatal Case of Bronchopneumonia. (Clinical Notes are Given in Table I, Case 7.)

Haldane,¹¹ using 18.5 volumes per cent of oxygen as equivalent to 100 per cent of hemoglobin. Two cubic centimeter samples were used and all determinations were made in duplicate within half an hour after collecting the sample. All of the

collections were made from bed patients, and in only a few instances was it necessary to insert the needle more than once. Care was used to cause the least possible pain, so there was practically no change in the rate of pulse or respiration during the operation. The blood is withdrawn much more slowly than when a tourniquet is used. It is important to apply very little suction, or bubbles of air will be drawn in around the piston, rendering the specimen useless.

The determinations made upon specimens taken during the hyperacute febrile period from the cases of influenza with an extreme grade of erythema, are shown in Table 1.

No abnormality is seen either in the oxygen content or in the oxygen unsaturation.

The results from the cases of bronchopneumonia are shown in Table 2.

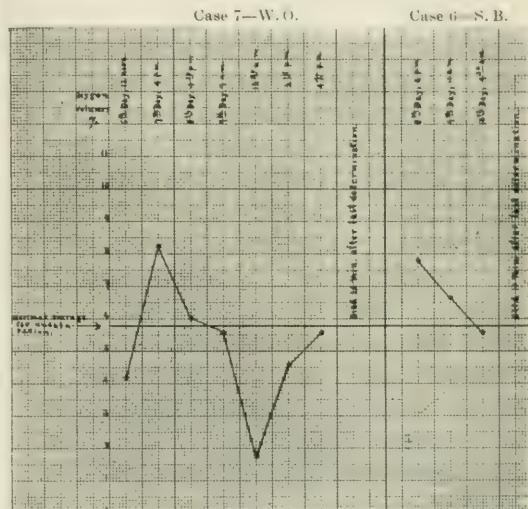


CHART 2.—Oxygen Unsaturation in Fatal Cases of Bronchopneumonia

The six cases of post-influenza bronchopneumonia (cases 1-6) which subsequently recovered, had definite physical evidence of consolidation during the course, with typical sputum, temperature curve and clinical phenomena. Four of them were exceedingly ill.

Three cases terminated fatally (cases 7-9). On one of these (case 9) there were but two determinations, the last nearly 24 hours before death. Both were within normal limits. On the other two cases, two or more determinations were made during the period of terminal collapse. In both there was a normal venous oxygen tension and capacity until the period of collapse occurred with its feeble, rapid pulse, rapid respirations and extreme cyanosis. Both the oxygen capacity and the oxygen content of the blood then fell rapidly and to a marked degree. The course of this case is shown on Chart 1.

¹⁰ Van Slyke, D. D.: Jour. Biol. Chem., 1918, XXXIII, 127.

¹¹ Haldane, J., and Smith, J. L.: Jour. Physiol., 1900, XXV, 331.

TABLE 1.—HYPERACUTE CASES OF INFLUENZA WITH MARKED ERYTHEMA, PROSTRATION, AND FEVER.
BLOOD CULTURES NEGATIVE

Case	Name	Day of disease	Hour	Oxygen content venous blood	Total oxygen capacity	Oxygen unsaturation	Hemoglobin calculated from oxygen capacity (18.5 vol. % = 100 %)	Temp.	Pulse	Resp.	Blood culture	Clinical data
1	H.	4	10:45 a. m.	14.35	18.97	4.62	102.0	100.2	92	24	0	Fourth day. Marked erythema. Extreme prostration.
2	L.	3	11:00 a. m.	11.77	17.39	5.62	93.9	99.	80	22	0	Third day. Face flushed. Physical examination negative.
3	R.	2	11:15 a. m.	13.18	15.83	2.65	85.6	102.8	100	20	0	Second day. Rather marked prostration. Lungs clear.
4	M.	2	10:30 a. m.	12.01	18.70	6.69	100.1	102.	98	20	0	Second day. Marked flush of face, neck and thorax, with throat eruption. Prostration. Lungs negative.

TABLE 2.—CASES OF BRONCHOPNEUMONIA FOLLOWING INFLUENZA

Case	Name	Day of disease	Hour	Oxygen content venous blood	Total oxygen capacity	Oxygen unsaturation	Hemoglobin calculated from oxygen capacity (18.5 vol. % = 100 %)	Temp.	Pulse	Resp.	Blood culture	Clinical data
1	S.B.F.	7	9:40 a. m.	15.33	18.68	3.35	101.0	101	90	26	0	Frank consolidation of both lowers. Profuse green purulent sputum. Marked flush of cheeks and upper chest. Alert and restless. Cyanosis. Resolution taking place on right. Thick green sputum. Slight cyanosis.
		12	11:35 a. m.	7.39	16.04	8.65	86.7	99.1	96	24		Left lower now resolving. Very pale. Looks worn out.
		17	10:15 a. m.	13.75	16.90	3.15	91.4	98.2	96	24		
2	Mrs.F.	8	10:40 a. m.	14.08	16.60	2.52	89.7	103.4	112	24	0	Cough with expectoration of small amount of blood-tinged sputum. Flush over cheeks and upper chest. Patch of consolidation at left lower.
3	D.O'B.	16	12:20 p. m.	7.46	14.20	6.74	76.8	99	100	24	0	Striking bluish plum color of lips, face and neck. Consolidation of both lowers.
		23	10:30 a. m.	5.68	11.27	5.59	60.9	98.6	100	22		Delayed resolution, both lowers. Peculiar color of face and neck persists.
4	E.W.	14	5:20 p. m.	10.52	16.60	6.08	89.7	104.8	100	32	0	Consolidation of right lower and middle lobes. Bloody sputum. Apprehensive.
		17	10:30 a. m.	10.19	13.65	3.46	73.8	98.3	80	26		First day following fall of temperature by crisis. Signs of resolution at right base.
5	M.A.	15?	10:30 a. m.	11.05	18.60	7.55	100.6	101.4	135	38	0	Empyema following pneumonia, with probably some consolidation remaining at right base. Flushed. Moderate cyanosis.
		18?	10:00 a. m.	15.25	18.55	3.30	100.2	99.8	100	34		Following operation. Rather marked cyanosis.
6	H.S.	4	12:30 p. m.	9.43	18.15	8.72	98.6	103.6	100	24	0	Bloody sputum. Consolidation of left lower. Well-marked cyanosis. Apprehensive.
		6	10:45 p. m.	9.71	18.10	8.39	96.2	99	88	20		Condition slightly improved. Still marked cyanosis. Less sputum. No difficulty in breathing.
7	W.O.	6	12:00 n.	12.88	17.10	4.22	92.4	101.9	104	44	0	Frank consolidation of both lowers. Jaundice. Difficult to rouse. Rapid, shallow respiration. No particular cyanosis.
		7	4:00 p. m.	8.25	16.50	8.25	89.2	104.4	120	52		No spread of consolidation. Somewhat brighter. Less jaundice.
		8	4:30 p. m.	9.80	15.85	6.05	85.7	103.4	120	56		Jaundice much less. Rarely coughs. No sputum. No spread of consolidation. Practically in coma.
		9	9:00 a. m.	5.38	11.00	5.62	59.5	103.4	124	60	Pneumococcus IV.	Evident collapse with well-marked, livid cyanosis. Cannot be roused. Many râles at both bases.
		9	12:20 p. m.	5.80	7.53	1.73	40.7	105.2	152	60		
		9	2:15 p. m.	3.84	8.44	4.60	45.6	140	56		
		9	4:40 p. m.	2.17	7.74	5.57	41.8	105.6	140	48		Patient died about ten minutes after this determination.
8	S.B.	8	2:00 p. m.	9.26	17.10	7.84	92.4	99.2	128	48	Pneumococcus, not grouped	Orthopnea. Cheeks flushed. Incomplete consolidation of both lowers, with many moist râles, especially on the left.
		9	10:00 a. m.	8.65	15.34	6.69	82.9	96.0	124	44		Subnormal temperature. Sweating. Cyanosis.
		10	9:30 a. m.	2.65	8.24	5.59	44.5	95.6	120	36		Frank consolidation of both lowers. Complete. Weak, collapsed, extreme cyanosis. Died 20 minutes later.
9	H.H.	4	10:10 p. m.	10.45	12.90	2.45	69.7	104.4	140	68	Pneumococcus, not grouped	Moderate cyanosis. Consolidation at right and left lowers, especially right.
		5	11:20 a. m.	8.07	11.98	3.91	64.8	105.5	180	72		Consolidation spreading. Died 24 hours later.

It is impossible in these two cases to explain the very great diminution in the oxygen-combining power and in the oxygen content of the blood just before death. Possibly the conversion of hemoglobin into methemoglobin progressed to a marked degree during the prolonged period of terminal collapse. If this be true, it would indicate that this conversion can proceed gradually to a marked degree without necessarily causing death, the circulatory mechanism to a certain point compensating for the lack of oxygen-carrying material, possibly by an increased velocity of the blood flow. On the other hand, it is possible that some other factor still unknown may play a part in altering the oxygen-carrying power of the blood.

The behavior of the curve for oxygen unsaturation is entirely unexpected. There is practically no deviation from the normal range of values up to the time of death.

In the five uncompensated cardiac cases studied by Lundsgaard² he found values for the oxygen unsaturation which were constantly higher than the normal values, ranging instead between 9.7 and 15.2 volumes per cent. He considered cyanosis one of the factors which have a very close relation to the amount of oxygen unsaturation in cardiac decompensation.

² Lundsgaard, C.: *Jour. Exp. Med.*, 1918, XXVII, 179.

sation. There seems, therefore, to be an essential difference between the effect upon the circulatory system which causes the cyanosis in cardiac disease and that which produced the cyanosis in these cases of bronchopneumonia.

CONCLUSION

1. The oxygen capacity and oxygen content of blood withdrawn from a peripheral arm vein have been determined in four cases of influenza during the hyperacute stage and in nine cases of bronchopneumonia following influenza.

2. Both oxygen content and oxygen unsaturation showed normal values in uncomplicated influenza cases.

3. In none of the cases of bronchopneumonia which recovered, and not until the terminal collapse in the fatal cases, has the venous oxygen content or the amount of oxygen unsaturation been abnormal. The values seem independent of temperature, pulse, respiration and extent of lung involvement.

4. In two fatal cases with septicemia, after the terminal collapse, there was a progressive fall in both the oxygen-combining power and the oxygen content of the venous blood, in general, parallel.

5. There was no increase at any stage of the disease in the values for the oxygen unsaturation of the blood.

BACTERIOLOGICAL FINDINGS IN EPIDEMIC INFLUENZA

By S. E. HOWARD, M. D.

(From the Medical Clinic of The Johns Hopkins Hospital)

The cultures reported in this paper were taken in the cases reported in the foregoing paper by Dr. Bloomfield and Dr. Harrop. At the onset of the epidemic an attempt was made to take cultures from the nasopharynx and the blood in every case of epidemic influenza admitted to The Johns Hopkins Hospital, and also to make cultures from the sputum whenever any was present. With the sudden increase in the number of cases it was impossible to carry out this plan. A special study was then made of patients who had a very sudden, severe onset, and who were admitted to the hospital wards immediately; cultures from the nasopharynx and the blood were taken from these patients as soon after admission as possible. Cultures from the nasopharynx were repeated in many of them during convalescence. From all patients who had any sputum an attempt was made to get a fresh specimen for culture. In all cases of pneumonia, which were considered critically ill, blood cultures were made; in most of these cases the cultures were repeated daily until marked improvement or death occurred.

The cultures from the nasopharynx were made on blood-agar plates. The agar contained about 5 per cent blood, and was poured into petri dishes with a diameter of $5\frac{1}{2}$ inches. To obtain the culture, a sterile swab was used, consisting of a piece of very stiff wire, the tip of which was wound with absorbent cotton, and bent at an angle of 80°. With the

tongue depressed, it was possible to slip the cotton-covered tip behind the uvula, thoroughly rub it over the nasopharynx, and extract it through the mouth, without coming in contact with the tongue or any parts of the buccal mucous membrane. This method of obtaining the culture seemed more satisfactory than using a West tube or inserting a swab through the nostrils. As soon as the swab was withdrawn, one side of a blood agar plate was streaked with it. A second sterile swab was rubbed first over the streak and then over the rest of the plate; by this method individual colonies of the bacteria present were obtained. The results of the cultures obtained from the nasopharynx by this technique are given in Table I.

The sputum for culture was obtained as follows: First, the patient was asked to clear his throat and to rinse his mouth thoroughly with Dobell's solution. Then he was asked to cough hard and to try to raise sputum from the lungs. Only sputum obtained after a good paroxysm of coughing was used. This was received in a sterile petri dish, carried immediately to the laboratory, and cultured as soon as possible, being kept on ice if any delay was necessary. Most of the specimens were thin, mucoid, often blood-tinged and difficult to wash. Whenever possible, the specimens were washed in six dishes of sterile salt solution; the more friable ones could only be washed three or four times. It was a striking fact

TABLE I.—NASOPHARYNX CULTURES—SUMMARY

Type of case	Results				Organisms present in small numbers
	Predominating organisms				
	Pneumococci	Green streptococci	<i>B. influenza</i>	Other organisms	
Cultures on admission from cases with hyperacute onset. (18 cases.)	2 cases. Both Group IV.	8 cases.	No cases.	4 cases had green colonies which may have been pneumococci or streptococci. Not identified. In 4 cases staph. albus predominated.	In 2 cases small gram-negative bacilli, morphologically like <i>B. influenza</i> , were seen in smears from cultures, but were not isolated in pure culture. Staph. albus, green streptococci and pneumococci also occurred in cultures in which they did not predominate.
Cultures from 12 of the above cases were taken during convalescence, about one week after admission. No pneumonias in this group.	The results of these cultures were practically identical with those of the cultures taken on admission, except that <i>more influenza bacilli were found</i> , though they were <i>never</i> present as the predominating organism. From two of these cases <i>B. influenza</i> was isolated in pure culture. In three others, small gram-negative bacilli, morphologically resembling <i>B. influenza</i> , were seen in smears from the original culture, but not isolated in pure culture.				
	Predominating organisms				Organisms present in small numbers
	Pneumococci	Green streptococci	<i>B. influenza</i>	Other organisms	
	Pneumococci	Green streptococci	<i>B. influenza</i>	Other organisms	
Cultures from 9 convalescents not previously cultured.	1 case. Group IV.	4 cases.	None.	Staphylococcus in 2 cases. Green colonies of pneumo. or strepto. not identified in 2 cases.	2 cases showed small gram-negative bacilli, morphologically resembling <i>B. influenza</i> . Not isolated in pure culture.
Cultures from 10 patients who did not have influenza.	3 cases of Group IV. 1 case of atypical Group II.	1 case.	1 case.	Staphylococcus in 2 cases. Unidentified pneumo. or strepto. in 1 case.	In 1 case small gram-negative bacilli morphologically resembling <i>B. influenza</i> were seen in smears from cultures, but not isolated in pure culture.

73 other nasopharynx cultures were taken at the onset of the epidemic, including all the first cases of epidemic influenza in the hospital. In only one of these did *B. influenza* predominate; in two others small gram-negative bacilli morphologically resembling it were seen, but not isolated in pure culture.

that the sputum we obtained in most of the cases was not the type of sputum which Pfeiffer¹ describes as typical of the cases in which he found *B. influenza*. In the few instances in which we found *B. influenza* as the predominating organism, the sputum was of a type different from that found in the majority of our cases; it was yellow-green in color, definitely purulent, tenacious and readily washed. These cultures were made on blood agar in petri dishes. The results of the sputum cultures are given in Table II.

Green streptococci, pneumococci and staphylococci also occurred in cultures in which they did not predominate.

In differentiating pneumococci (Type IV) from green streptococci, bile solubility was adopted as the criterion. Some partiality soluble strains were found. Most of the strains classified as "green streptococci" formed long chains in meat infusion broth and produced relatively slight turbidity, but an abundant sediment. Most of the bile soluble strains caused diffuse turbidity with a variable amount of sediment. Morphologically, the majority of the insoluble forms were more or less lance-shaped; many of them were markedly elongated, so as to be almost bacillary in type; more so than the typical pneumococcus. On blood agar plates, in-

dividual colonies tended to be smaller and less moist than typical pneumococcus colonies; and on blood-agar slants

TABLE II.—SPUTUM CULTURES—SUMMARY
(Cultures were done in 36 cases)

Predominating organisms			
Pneumococci	Green streptococci	<i>B. influenza</i>	Other organisms
Group IV. 4 cases.	18 cases.	3 cases.	6 cases—green colonies, which may have been either pneumococci or green streptococci; the organisms were not identified.
Group III. 1 case. Patient had Group III pneumonia previous to present illness.			1 case—a pure culture of staphylococcus aureus was present.
Groups I & II. None.			In the remaining cases, mic. catarrhalis or staph. albus predominated.

ORGANISMS PRESENT BUT NOT PREDOMINATING

In 13 cultures in which *B. influenza* did not predominate small gram-negative bacilli, which morphologically were like *B. influenza*, were seen in smears from the original culture or in fresh sputum. In these cases we were unable to isolate this organism in pure culture, as very few of these bacilli were present.

¹ Pfeiffer, R., and Beck, M.: Weitere Mittheilungen über den Erreger der Influenza. Deutsch. med. Wchnschr., 1892, XX, 465.

there was a greater tendency to diffuse greenish discoloration of the agar. All of the green streptococci tested were readily phagocytizable in normal serum. Those isolated from the

TABLE III.—BLOOD CULTURES—SUMMARY

Type of case	Result
Uncomplicated cases at onset.— Cases with particularly acute onset. Cultures made in 18 cases on day of admission.	No growth in any culture.
Patients with pneumonia who recovered.—Cultures taken when patients were in critical condition. 28 cultures from 12 patients.	No growth in any culture.
Patients with pneumonia who died.—Cultures taken within 24 hours of death in all but 2 cases. 27 cultures in 13 cases.	3 cases.—Pneumococcus Group IV, 23+%. 1 case.—Pneumococcus Group III, 7+%. 1 case.—Pneumococcus (Group not determined), 7+%. 1 case.—Hemolytic streptococcus, 7+%. 7 cases.—No growth, 55+%.

nasopharynx of control cases seemed identical with strains obtained from influenza patients.

In making cultures from the blood, the usual technique was employed. In addition to pouring blood-agar plates and adding the blood to glucose broth and litmus milk, in many

cases blood was added to ascitic-meat-infusion broth. The results of the blood cultures are given in Table III.

In conclusion, we feel that none of the organisms isolated may be regarded as the cause of epidemic influenza. Our own results, compared with the summary of European literature on this subject² and the more recent work of Nuzum, *et al.*,³ Strouse and Bloch,⁴ etc., convince us that the *B. influenza* of Pfeiffer is merely a secondary invader, though in some localities, as in the cases reported by Keegan,⁵ it may be a frequent cause of terminal bronchopneumonia. The other organisms isolated may also be regarded either as normal inhabitants of the mouth or as secondary invaders. The primary cause of epidemic influenza, we believe, is still unknown.

I am indebted to Dr. Charles W. Young for the isolation and identification of organisms from many of these cultures.

² Abstracts of Foreign Literature Compiled by British Medical Research Committee. Jour. Am. Med. Assn., 1918, LXXI, 1573.

³ Nuzum, J. W.; Pilot, I.; Stangl, F. H.; Bonar, B. E.: Pandemic Influenza and Pneumonia in a Large Civil Hospital. Jour. Am. Med. Assn., 1918, LXXI, 1562.

⁴ Strouse, S., and Bloch, L.: Notes on the Present Epidemic of Respiratory Disease. Jour. Am. Med. Assn., 1918, LXXI, 1568.

⁵ Keegan, J. J.: The Prevailing Pandemic of Influenza. Jour. Am. Med. Assn., 1918, LXXI, 1051.

ECTOPIC PREGNANCY

By H. M. N. WYNN.

Resident Gynecologist, The Johns Hopkins Hospital

INCIDENCE

In the 27 years from 1890 to 1916 inclusive, there have been 303 patients with ectopic pregnancy in the Gynecological Service of The Johns Hopkins Hospital who were operated upon. There have been 22,688 patients admitted to the Gynecological Service during the 27 years, of which 303 had extrauterine pregnancies, an incidence of 1.3%.

TABLE SHOWING THE NUMBER OF PATIENTS WITH EXTRAUTERINE PREGNANCIES EACH YEAR

Year	Number of patients	Year	Number of patients	Year	Number of patients	Year	Number of patients
1890	2	1896	6	1902	8	1908	23
1891	3	1897	1	1903	15	1909	23
1892	4	1898	8	1904	23	1910	13
1893	8	1899	7	1905	23	1911	15
1894	7	1900	10	1906	13	1912	11
1895	3	1901	10	1907	16	1913	11
						Total	303

Race.—Negroes, 101; white, 202. Total, 303.

Of these 22,688 patients, 17,112 were white and 5,576 were negroes. There were 202 cases of extrauterine pregnancy among the whites (1.16%) and 101 among the negroes (1.91%).

AGE

Of this series of cases the age was recorded 300 times. The youngest patient was a 15-year-old white girl, married seven months previously to admission and never pregnant before. An unruptured left tubal pregnancy was removed at operation. The oldest patient was a 45-year-old negress, who had given birth to three full-term children. At operation a full-term lithopedion, which had been in the abdomen for four years was removed (Reported by J. G. Clark, The Johns Hopkins Hospital Bulletin, 1897, VIII, and in Kelly's Operative Gynecology, Vol. II). Of this series 182 (61%) occurred in the decade 24 to 33 years inclusive. Seven patients were under 20 years and ten were over 40 years of age.

TABLE SHOWING AGES OF 300 PATIENTS

Age	Number of patients	Age	Number of patients	Age	Number of patients	Age	Number of patients
15	1	22	10	28	25	34	11
17	1	23	11	29	17	35	13
18	3	24	22	30	18	36	9
19	2	25	18	31	17	37	6
20	6	26	12	32	13	38	8
21	12	27	20	33	20	39	11
						40	4
						41	2
						42	4
						43	2
						44	1
						45	1

MARITAL HISTORY

In a series of 284 there were 14 unmarried, two widows and nine twice married.

TABLE SHOWING TIME OF ADMISSION AFTER MARRIAGE

Time married	Number of patients	Time married	Number of patients	Time married	Number of patients	Time married	Number of patients
		<i>yrs.</i>		<i>yrs.</i>		<i>yrs.</i>	
2 wks...	1	1	9	9	8	18	9
4 wks...	1	2	22	10	14	19	3
6 wks...	1	3	18	11	9	20	7
2 mos...	1	4	13	12	17	21	6
4 mos...	1	5	15	13	11	22	2
5 mos...	1	6	12	14	8	23	3
7 mos...	1	7	21	15	9	26	1
8 mos...	1	8	18	16	6	27	1
			17	8	Total	268	

PREVIOUS PREGNANCIES

In the histories of 275 patients, the number of pregnancies prior to the ectopic pregnancy was recorded. In 57 (21%) there had been no previous pregnancy and of the 218 (79%) who had been pregnant before, 207 (95%), 75% of the whole series, had given birth to full-term babies and 11 (5%), 4% of the whole series, had had only miscarriages. Instrumental deliveries had been performed on 19 patients (9% of those who had had full-term pregnancies). Histories of prolonged puerperia associated with chills, fever and abdominal pain were obtained from 38 patients (17.5% of all patients previously pregnant).

TABLE SHOWING NUMBER OF PREVIOUS PREGNANCIES

Number of miscarriages	Number of patients	Number of children	Number of patients	Total pregnancies	Number of patients
1	65	1	77	0	57
2	25	2	32	1	67
3	8	3	27	2	42
4	5	4	21	3	22
5	2	5	17	4	22
6	2	6	14	5	16
		7	8	6	16
		8	2	7	13
		9	2	8	8
		10	3	9	2
		11	1	10	3
		12	0	11	1
		13	1	12	1
		14	2	13	1
				14	1
				15	2
				16	1
				Total 207	
					Total 275

The interval between the last pregnancy and admission to the hospital for an ectopic pregnancy was noted in the histories of 226 patients, the shortest interval being three months and the longest 19 years. The interval was between one and seven years in 168 patients (74%).

TABLE SHOWING THE INTERVAL BETWEEN THE LAST PREGNANCY AND ADMISSION TO THE HOSPITAL FOR ECTOPIC PREGNANCY

Time	Number of patients	Time	Number of patients	Time	Number of patients	Time	Number of patients	Time	Number of patients
<i>mos.</i>		<i>mos.</i>		<i>yrs.</i>		<i>yrs.</i>		<i>yrs.</i>	
3	1	9	5	3	23	9	5	15	3
4	1	10	1	4	22	10	8	16	1
5	4	11	2	5	13	11	4	17	1
6	4	12	20	6	20	12	6	18	1
7	1	18	15	7	19	13	1	19	2
8	1	2	36	8	5	14	1	Total	226

PREVIOUS OPERATIONS

Forty-five patients had had operations prior to admission for ectopic pregnancy.

Dilatation and curettage had been performed on 15 patients for bleeding caused by the ectopic pregnancy; two of these operations were done in this hospital. One patient was curetted twice before admission for bleeding caused by the ectopic pregnancy.

Curettage was performed on 12 patients, from one to five years before their admission and simple dilatation of the cervix twice for sterility.

Incision of Bartholin gland abscess, five years before; one patient.

Pelvic puncture for inflammatory disease; three patients.

Exploratory laparotomy five years before; one patient.

Multiple myomectomy five years before; one patient.

Ovarian tumor removed; one patient.

Tumor removed and *appendectomy*; six years before; one patient.

Paroovarian cystectomy, right; *suspension of uterus*; *appendectomy*; two years before (Gyn. No. 16,409).

Suspension of uterus and *appendectomy*; 18 months before (Gyn. No. 15,751).

Salpingo-oöphorectomy, left, and *appendectomy*; one and two years ago, for chronic pelvic inflammatory disease; two patients.

Salpingo-oöphorectomy, right, and *appendectomy*; one patient.

Appendectomy (only); three patients.

Appendectomy and *nephroperxy* were done in another city on one patient for the symptoms caused by a right tubal pregnancy about six and eight weeks prior to admission to this hospital.

Five patients have been operated upon twice in this hospital for ectopic pregnancy.

Pelvic puncture, once.

Salpingectomy (alone), twice.

Salpingo-oöphorectomy, twice.

COMPLAINT

The symptoms that patients complained of on admission were as follows:

Bleeding	93
Pain, general abdominal or not specified	99
Pain in lower abdomen	69
Pain in right lower quadrant of abdomen	33
Pain in left lower quadrant of abdomen	33
Pain in back	20
Pain designated as "bearing-down," 4 times; and as "cramp-like," 4 times.	
Tumor in abdomen	17
Tumor in right lower quadrant of abdomen	1
Tumor in left lower quadrant of abdomen	4
Swelling of abdomen	3
Tenderness of abdomen	4

Pregnancy	2
Miscarriage	1
Amenorrhœa	1
Dysmenorrhœa	2
Vomiting	9
Nausea	6
Diarrhœa	1
Pain on defecation	1
Dysuria	2
Pollakiuria	1
Fainting	1

From the foregoing list we see that the most common causes for which these patients seek medical attention are pain, complained of by 254 (84%) bleeding, complained of by 93 (31%) and tumor, complained of by 22 patients (7%).

SYMPTOMS

Onset (1) Acute without prodromal symptoms other than bleeding or a missed period.....	146	(48%)
(2) Acute with prodromal symptoms.....	72	(24%)
(3) Gradual without acute attacks.....	84	(28%)
Irregular bleeding	229	(76%)
Nausea	146	(48%)
Vomiting	126	(42%)
Tumor	45	(15%)
Fainting	38	(13%)
Fever	29	(10%)
Chills	12	(4%)
Weakness	87	(29%)
Defecation painful	28	(9%)
Urinary frequency	40	(13%)
Burning on voiding	27	(9%)
Pain on voiding	87	(29%)
Loss of weight.....	6	(2%)
Bad taste in mouth.....	3	(1%)
Patients believing themselves to be pregnant.....	11	
Patients not suspecting pregnancy.....	3	
Patients suspecting an abortion.....	1	
Patients who had felt life.....	1	
Patients having a sensation of fluid in the abdomen.....	1	
Patients who had passed complete casts of the uterus.....	2	
Patients complaining of pain in the abdomen not otherwise qualified	131	(43%)
Pain, general abdominal	21	(7%)
Pain, limited to the lower abdomen.....	28	(9%)
Pain, limited to the lower left quadrant.....	43	(14%)
Pain, limited to the lower right quadrant.....	41	(13%)
Abdominal pain over pelvis, with pain in the epigastrium	2	
Abdominal pain over pelvis, with pain in the umbilical region	1	
Abdominal pain over pelvis, with pain in the bladder.....	1	
Abdominal pain over pelvis, with pain in the rectum.....	2	
Abdominal pain over pelvis, with pain in the flanks.....	2	
Abdominal pain over pelvis, with pain in the thighs.....	1	
Abdominal pain over pelvis, with pain in the legs.....	2	
Abdominal pain over pelvis, with pain in the right shoulder	2	
Abdominal pain over pelvis, with pain in the chest.....	1	
Patients complaining of backache.....	19	
Patients complaining of headache.....	2	

Pain.—The symptoms that a patient considers as sufficiently unusual to cause her to seek medical attention are produced in the vast majority of cases by intraperitoneal bleeding. A history of abdominal pain was procured from

300 patients (99%), the other three patients stated positively that there had been no abdominal pain or discomfort and they came to the clinic on account of irregular bleeding. In each of these three patients an unruptured tubal pregnancy was found at operation, but no evidence of any clot or free blood in the peritoneal cavity.

The onset of the symptoms may be acute without other prodromal symptoms, although there is usually a history of a missed period or of irregular bleeding. In a second type there is an acute attack following prodromal symptoms, which the patient sometimes ascribes to her pregnancy. A third type of patient gives a history of gradual onset without an acute attack.

Recurring attacks of pain occurred in 102 cases (34%); seventeen patients complained especially of soreness and tenderness, rather than of definite pains. In several instances the pain was of several years' duration, generally with a recent exacerbation, but in each instance at operation some other condition, usually chronic pelvic inflammatory disease, was also present.

The pains seem rarely to radiate. The character of the pain was described as violent, agonizing or severe in 90 cases, cramping in 41, colicky in four, bearing down in 14, labor-like in nine, shooting, cutting or sticking in six and as dull or aching in 29.

Pain or irritation in the rectum and bladder occur after intraperitoneal hemorrhage, most often when clots have collected in the pelvis and adhesions have formed. Pain and vaginal bleeding often occur about the same time. Mysey (St. Paul Med. Jour., 1914, XVI, 588) states that pain on defecation is almost pathognomonic of the condition, but in our experience, this symptom is also frequently present in cases of pelvic inflammatory disease.

MENSTRUAL HISTORY

One hundred and three patients (34%) stated definitely that they had missed one or more periods; and 31 (10%) said that their last period had been overdue for from one to five weeks, while 52 (17%) had noticed that the last period was abnormal in some other respect.

Number of periods missed	Number of patients	Number of periods missed	Number of patients
1	42	7	1
2	34	8	2
3	14	9	0
4	2	10	3
5	4	11	1
6	0	Total.....	103 patients.

Increased frequency of menstruation.....	14
Constant bleeding since last period.....	60
No irregular bleeding.....	49
No irregular bleeding and no periods missed.....	18
Periods normally regular.....	210
Periods normally irregular.....	30

Last menstrual period:	
Overdue 1 week.....	11
Overdue 2 weeks.....	16
Overdue 3 weeks.....	2
Overdue 4 weeks.....	1
Overdue 5 weeks.....	1
Ahead of regular time.....	12
Shorter than usual.....	5
Longer than usual.....	20
Flow decreased.....	13
Flow increased.....	9
Color abnormal.....	5

Nausea and vomiting occurred in a few cases, as in normally pregnant women and the patients with these symptoms considered themselves pregnant. In the great majority, however, there was a history pointing to intraperitoneal hemorrhage before nausea or vomiting had occurred.

Abdominal masses were noticed by the patients in cases of advanced pregnancy and where a walled-off hematocoele was present.

Fainting occurred in some cases where there was profuse intraperitoneal hemorrhage.

Chills and fever were unusual symptoms and always suggested the gravest complications.

Weakness is generally present in the more anæmic.

Loss of weight was noticed only in advanced tubal pregnancy, as also was the complaint of a bad taste in the mouth.

The notes in our histories as to whether the patient considered herself pregnant are very incomplete, and no conclusions can be drawn from them except that not all believed that they were pregnant.

SIGNS

In the following tabulation of physical signs, it is notable that many of the presumptive signs of intrauterine pregnancy are not present in the majority of this series of ectopic pregnancies. In the larger percentage of the cases in which the table gives "a softened and enlarged cervix or fundus" the notes were "slightly softened" or "slightly enlarged" and often there was a difference of opinion in those cases examined by two men. We believe that most cases of tubal pregnancy show no very definite gross changes in the cervix and uterine body, unless the fetus is living. In no case was a positive Hegar's sign recorded. Vaginal cyanosis was not marked in any case.

The usual absence of definite muscle spasm or rigidity is in accordance with the signs of most pelvic diseases and, where present, there was invariably blood in the peritoneal cavity, not confined to the pelvis. Voluntary resistance to deep pressure was a very common sign.

Abdominal tenderness was frequently absent in cases of pelvic hematocoele; in unruptured tubal pregnancy and in advanced cases, but in patients who had had a recent severe hemorrhage, the abdomen was generally exquisitely tender.

The figures recorded on pelvic tenderness are undoubtedly too low. Certainly in those patients that have been under my observation, there is usually marked tenderness, and, especially when the pelvis is filled with recent clots, there is an

even greater degree of tenderness than is found in cases of pelvic abscess. I have seen two cases of unruptured tubal pregnancy in which firm bimanual compression of the mass elicited no complaint or discomfort, but they are very unusual.

SIGNS ON PHYSICAL EXAMINATION

Shock (extreme).....	15
Breasts:	
Lactating.....	7
Colostrum present.....	46 (15%)
Abdomen:	
Distention.....	90 (30%)
Free fluid.....	33 (10%)
Mass.....	72 (24%)
Tenderness, general.....	21 (7%)
Tenderness, limited to lower abdomen.....	71 (23%)
Tenderness, limited to lower right quadrant.....	52 (17%)
Tenderness, limited to lower left quadrant.....	39 (13%)
Muscle spasm.....	11 (4%)
Rigidity.....	17 (6%)
Pelvis:	
Vaginal cyanosis.....	6 (2%)
Bloody discharge from vagina.....	85 (25%)
Cervix softened.....	85 (25%)
Cervix enlarged.....	48 (16%)
Fundus softened.....	15 (5%)
Fundus enlarged.....	86 (25%)
Mass, boggy.....	83 (24%)
Mass, firm.....	38 (12%)
Mass, cystic.....	40 (13%)
Blood clot crepitus.....	21 (7%)
Tenderness.....	146 (48%)

HEMOGLOBIN AND LEUCOCYTE COUNT

Unfortunately, hemoglobin determinations and leucocyte counts were not done in many of the cases. It is to be remembered that the lowest point of the hemoglobin curve is not obtained until from 48 to 72 hours after an acute hemorrhage (Dunn & Wynne, *JOHN HOPKINS HOSPITAL BULLETIN*, XXIX, No. 323, January, 1918). On this account, the degree of anæmia caused by the acute hemorrhage is not determined as a rule before operation. A high leucocyte count is usually found shortly after acute intraperitoneal hemorrhage and cannot by itself be considered an indication of infection. In our small series of leucocyte counts, there were between 20,000 and 30,000 leucocytes in 8 cases (10%) and between 10,000 and 20,000 in 39 cases (47.5%). This observation agrees with those reported by other authors.

HEMOGLOBIN BEFORE OPERATION

Per cent of hemoglobin	Number of patients	Per cent of hemoglobin	Number of patients
15	1	60-70	18
20-30	3	70-80	20
30-40	13	80-90	16
40-50	7	90-100	9
50-60	19		

Total number of patients on whose blood hemoglobin determinations were done prior to operation, 106.

LEUCOCYTE COUNT BEFORE OPERATION

W. B. C.	No. of patients	W. B. C.	No. of patients	W. B. C.	No. of patients
3,000	1	10,000-11,000	12	16,000-17,000	3
5,000-6,000	2	11,000-12,000	1	17,000-18,000	1
6,000-7,000	6	12,000-13,000	8	18,000-19,000	2
7,000-8,000	6	13,000-14,000	2	20,000-21,000	1
8,000-9,000	11	14,000-15,000	4	22,000-23,000	5
9,000-10,000	9	15,000-16,000	6	30,000-	2

Total number of patients on whom leucocyte counts were made before operation, 82.

TEMPERATURE AND PULSE

The temperature on admission to the hospital was less than 101° F. in 161 (91%) of a series of 180 consecutive admissions for ectopic gestation and the pulse was less than 130 per minute in the same number of patients. The majority showed some increase in both pulse rate and temperature.

TEMPERATURE AND PULSE ON ADMISSION TO THE HOSPITAL OF 180 CONSECUTIVE PATIENTS

Temperature	No. of patients	Temperature	No. of patients	Temperature	No. of patients
Did not register...	1	99.5-100	29	102.0-102.5	5
97.0-98.0	5	100.0-100.5	30	102.5-103	0
98.0-98.5	30	100.5-101	8	103.0-103.5	1
98.5-99.0	26	101.0-101.5	5	103.5-104	2
99.0-99.5	41	101.5-102	3		

Pulse	No. of patients	Pulse	No. of patients	Pulse	No. of patients
60-70	4	110-120	16	150-160	0
70-80	9	120-130	21	160-170	2
80-90	22	130-140	7	170-180	1
90-100	46	140-150	5	Could not be counted	1
100-110	52				

PRE-OPERATIVE DIAGNOSIS

The pre-operative diagnosis was recorded on the history in 212 cases. The correct diagnosis was made on admission in 98 cases (46%) and confirmed on examination after the patients had been anesthetized for operation. Twelve additional cases were diagnosed correctly only after the patients were under anesthesia, while a probable diagnosis of extrauterine pregnancy was made in five other cases, one of which had a posterior vaginal coeliotomy performed before the laparotomy for confirmation of the diagnosis. In 28 other cases the condition was suspected but not definitely diagnosed until some operative procedure had been performed. In 69 cases (33%) the extrauterine pregnancy was not diagnosed, although in a number of these cases some other pathological condition present was diagnosed correctly. The diagnoses recorded were made by some member of the resident staff in the large majority of the cases.

TABLE OF DIAGNOSES BEFORE OPERATION

Extrauterine pregnancy (on admission examination)....	98 cases
Extrauterine pregnancy (on examination under anesthesia).....	12 cases

Extrauterine pregnancy (probable diagnosis).....	4 cases
Extrauterine pregnancy (after exploratory puncture)....	1 case
Retained membranes of extrauterine pregnancy.....	11 cases
Pelvic abscess or extrauterine pregnancy.....	6 cases
Chronic pelvic inflammatory disease or extrauterine pregnancy.....	6 cases
Appendix abscess or extrauterine pregnancy.....	1 case
Chronic appendicitis or extrauterine pregnancy.....	1 case
Cystoma of ovary or extrauterine pregnancy.....	1 case
Myoma uteri or extrauterine pregnancy.....	1 case
Calcified myoma or lithopedion.....	1 case
Fibro-cystoma.....	1 case
Ovarian cyst with twisted pedicle.....	1 case
Multilocular cystic ovary.....	1 case
Ovarian tumor.....	1 case
Ovarian tumor (malignant).....	1 case
Papillomatous cyst of ovary.....	1 case
Parovarian cyst.....	1 case
Myomata uteri.....	5 cases
Myomata uteri with pregnancy.....	2 cases
Myomata uteri, cystic, or sarcoma of uterus.....	1 case
Myomata uteri, cystic, or anglioma of uterus.....	1 case
Myomata uteri with adherent dermoid cyst.....	1 case
Pelvic abscess.....	11 cases
Pelvic abscess with general peritonitis.....	1 case
Pelvic abscess or appendix abscess.....	1 case
Chronic pelvic inflammatory disease.....	20 cases
Subacute pelvic inflammatory disease.....	2 cases
Acute pelvic inflammatory disease.....	1 case
Chronic appendicitis.....	2 cases
General peritonitis.....	1 case
Retained membranes.....	2 cases
Abortion, infected.....	1 case
Miscarriage due to retroposition of the uterus.....	1 case
Pregnancy.....	1 case
Retroposition of the uterus.....	2 cases
Chronic pelvic inflammatory disease.....	1 case
Tubo-ovarian abscess.....	
Ovarian cyst.....	
Submucous myoma, cystic.....	
Ovarian tumor.....	1 case
Extrauterine pregnancy.....	
Chronic pelvic inflammatory disease.....	1 case
Papilocystoma of ovaries.....	
Tuberculous pelvic inflammatory disease.....	
Pelvic inflammatory disease with ovarian cyst.....	3 cases
"No diagnosis made".....	

We do not believe that the flat-footed diagnosis of extrauterine pregnancy is as simple as many writers consider it. In making an estimate of the percentage of faulty diagnoses, we should also include those cases diagnosed as extrauterine pregnancy which, at operation, prove to be another condition. In this clinic the latter class of cases is numerous. In private practice among more intelligent patients, there should be a higher percentage of correct diagnoses made than in a free clinic. The classical case of an acute ruptured ectopic pregnancy is usually clear if a satisfactory history can be obtained, but there are a great many cases in which the history points equally well to pelvic inflammatory disease. The latter disease also gives symptoms that not infrequently strongly suggest extrauterine pregnancy. Cases with unilateral inflammatory disease are seen in this clinic fully as often as extrauterine pregnancies and may be very puzzling. The

differential diagnosis in this class of cases is often difficult even when a careful history has been taken.

Very often there are other conditions present that make a positive diagnosis practically impossible. Another stumbling-block is encountered occasionally in patients who have had an early abortion with retained membranes and have a cystic ovary on one side. We have seen three cases of this character which were correctly diagnosed by one or more members of the staff, but which were considered to be unruptured extrauterine pregnancies by other members who examined the patients under equally favorable circumstances.

There are occasional cases in which the diagnosis is in doubt even after operation has been performed, as in the following:

Gyn. No. 22180. The patient was a white woman, age 33; she was admitted to the hospital May 16, 1916, complaining of "bowel trouble."

Married 12 years; three children, youngest six years of age. No miscarriages. Labors normal. Fever for two weeks beginning in the fourth week following the first labor; otherwise the puerperia were normal.

Last menstrual period February, 1916; last preceding October, 1915. Miscarriage on January 1, 1916, after slight vaginal bleeding for the preceding week. A curettage was done by her family physician January 2 and the patient was told that "the afterbirth was perfect." No fetus was seen. A period normal, except slightly prolonged, began on February 7 and lasted seven days. On February 21 an appendectomy and a curettage were performed. The surgeon who operated said that the uterus, tubes and ovaries were normal at that time. No pain followed the operation until April 6, when she had a gradually increasing pain in the lower abdomen and back. This became quite severe, but lasted only one day. The abdomen felt sore for the following three days. She had no further abdominal pain until May 13 at 6 p. m., when she began to have pain in the left lower quadrant of the abdomen, similar to the previous attack. There had been slight vaginal bleeding for three days prior to this attack, during which the bleeding increased considerably. This attack of pain lasted 36 hours.

P. E.—Pulse 100. Temperature 99.6°, May 15, 1916. W. B. C., 19,000. Hbg. 95%.

Abdominal tenderness marked in the left lower quadrant and less marked in the right lower quadrant. Moderate rigidity below the umbilicus. A firm, smooth mass can be felt about half way between the umbilicus and pubis.

Pelvic Examination.—A bloody vaginal discharge is present. Cervix slightly softened and slightly enlarged. The tumor described above seems to be the uterus. A moderately firm mass, which is tender, can be felt in the left fornix. Blood clot crepitus in the cul-de-sac.

Diagnosis.—Extrauterine pregnancy, left, probably with beginning tubal abortion.

February 17, 1916.—Operation. A pelvic puncture was performed and about three ounces of old black blood was evacuated from the pelvis. The patient was immediately

prepared for laparotomy. There was a considerable amount of old blood in the abdomen. The tubes were found densely adherent in the cul-de-sac, the fimbriated ends were open, both tubes were considerably enlarged and oedematous. No fetal or placental tissue could be found, nor was there any visible site of an ectopic pregnancy in either tube. The tubes were released from adhesions and a cigarette drain placed through the cul-de-sac. There was a good deal of fresh bleeding during the operation. The patient was discharged June 16 after a rather prolonged convalescence. At the time of discharge the uterus was still enlarged, but there were no pelvic masses or tenderness.

TREATMENT

The treatment of our cases has been operative, either by the abdominal or vaginal routes. In several cases posterior vaginal coeliotomy has been performed for diagnosis. Pelvic puncture has been employed for pelvic hematocoele in a number of cases, although in 60% of these cases a laparotomy was performed immediately afterwards.

TABLE OF OPERATIONS

Vaginal (only)	24 cases (8%)
Pelvic puncture (only)	16 cases
Pelvic puncture with laparotomy (for hemorrhage following puncture, 4)	24 cases
Pelvic puncture with dilatation and curettage	3 cases
Dilatation and curettage with laparotomy	5 cases
Vaginal salpingectomy	1 case
Exploratory above Poupart's ligament into sac	3 cases
Laparotomy	279 cases (92%)
Abdominal incision of sac with drain-	
age	5 cases
Removal of fetus and placenta	6 cases
Salpingectomy (unilateral)	180 cases
Salpingectomy (bilateral)	56 cases
Resection of one tube	1 case
Puncture of hematosalpinx	2 cases
Total extirpation of sac and contents	12 cases
Partial extirpation of sac	1 case
Oöphorectomy (unilateral)	108 cases
Oöphorectomy (bilateral)	24 cases
Resection of one ovary	11 cases
Ovarian cyst tapped	1 case
Hysterectomy	30 cases
Resection of uterine cornu	7 cases
Myomectomy	5 cases
Excision of accessory tube	1 case
Ligation of remaining tube	1 case
Excision of abscess sac	1 case
Suspension of uterus	10 cases
Excision of mesenteric cyst	1 case
Excision of umbilical hernia	1 case
Resection of omentum	1 case
Release of intestinal adhesions	5 cases
Suture of rectum	3 cases
Suture of sigmoid	1 case
Resection of ileum	3 cases
Lateral anastomosis	3 cases
Additional: Perineal repair	6 cases
Additional: Perineal repair with suture of rectal sphincter	2 cases

Laparotomy by the abdominal route has been preferred in all cases except those in which there was a pelvic hematocoele with symptoms and signs indicating infection. In such cases, pelvic puncture and drainage is usually a safer procedure, although a secondary laparotomy may be necessary later for continued pain.

The majority of our patients have entered the hospital after examination in the Out-Patient Department and have been operated upon on the day following admission, unless they were in serious condition at the time of admission, when immediate operation has been performed, with very satisfactory results. One patient whose case has been previously reported by Richardson (JOHNS HOPKINS HOSPITAL BULLETIN) was in very extreme shock when admitted to the hospital and was treated expectantly. However, three days later, operation became imperative on account of marked abdominal distention and she died on the third day after the operation. Richardson thought this patient could have been operated upon the day following admission, when she had recovered somewhat from the primary shock and before serious distention had set in.

Whenever other pathological conditions demanding operation were present, they were included in the operative treatment, when the patient's condition justified a prolongation of the procedure.

Peritoneal Toilet.—In the majority of our cases the peritoneal cavity had been cleaned of blood and clot as well as possible. In 259 cases the peritoneal cavity was cleaned of blood and clot, and in eight cases no attempt was made to evacuate blood. We believe that the convalescence is more satisfactory when the blood is carefully removed.

Irrigation.—The peritoneal cavity was irrigated in 31 cases, sterile normal salt solution being used in 35 cases and sterile water in two cases. In recent years this practice has been discontinued.

The sac has been irrigated following pelvic puncture in nine cases, but this procedure has been abandoned on account of the danger of breaking through the wall and filling the peritoneal cavity with the fluid, as occurred in one case and resulted in a general peritonitis. This patient recovered after a secondary operation for drainage of the abdomen.

Drainage.—Primary drainage has been used in 150 cases; glass tubes were employed twice and in the remainder gauze usually in the form of a cigarette drain. The drains are preferably placed through the cul-de-sac into the vagina, rather than through the abdominal wall (38 cases were drained through the abdominal incision). At the present time drains are not employed unless there is some evidence of infection in the pelvis or a general ooze following the release of adhesions.

Stimulants.—Salt solution administered subcutaneously is depended upon for stimulation during operation and has been employed in 56 cases. Salt solution by rectum has been used in 13 cases and with equal parts of coffee in four cases. The peritoneal cavity was filled with salt solution before

closing the abdomen in 34 cases, but this procedure has been discontinued, as it seems to favor post-operative distention and generally increases the patient's discomfort, as well as spreading infection over the entire abdomen, if any should be present. In the case of one patient with very serious shock, an infusion of normal salt solution was administered through the radial artery and resulted in gangrene of the hand. In a few cases drug stimulants have been used hypodermically, strychnine in 16 cases, digitalis in three cases and brandy and ether in one case.

Transfusion of blood has not been used in any case included in this series. Very satisfactory results, however, have been reported by others who have used both direct and indirect transfusion, but sometimes there is no time to match the bloods of donor and recipient and a severe reaction following the transfusion may be fatal. The majority of these acutely ruptured cases can be stimulated sufficiently with subcutaneous infusions of large quantities of salt solution to tide them over the immediate shock. As all these patients are of ages most favorable for operative risk and as a rule have been in good health prior to the acute onset, they usually will recover if stimulated with salt solution for the first few hours.

Lichtenstein (Muench. Med. Wchnschr., 1915, LXII, 1597) reports eight cases treated by reinjection of the blood found in the patient's abdomen after defibrination and dilution with salt solution 3:2, a procedure open to criticism.

The intravenous injection of 7% acacia in distilled water, filtered and sterilized by boiling, will probably prove to be of great value in those cases in which there is severe shock due to great loss of blood volume (Rous-Wilson, Jour. Am. Med. Assn., January 26, 1918). We have used this preparation in one case in which there was an abundant hemorrhage at operation and severe shock, with gratifying results.

There are, of course, patients in such serious shock when first seen that operation is contra-indicated. In these cases shock must be combated by some of the methods mentioned above, but as soon as the patient is in condition to stand operation, it should not be delayed.

The time consumed in operating is shown in the table for 255 cases.

TABLE SHOWING THE DURATION OF OPERATIONS

Time min.	Number of cases	Time		Number of cases	Time		Number of cases
		hrs.	min.		hrs.	min.	
5	3		45	22	1	25	4
10	6		50	23	1	30	4
15	4		55	14	1	40	2
20	10	1		21	1	45	4
25	14	1	5	11	1	50	2
30	21	1	10	17	1	55	2
35	29	1	15	6	2		2
40	23	1	20	8	2	10	2
					2	25	1

Total, 255 operations.

All operations consuming less than 20 minutes were pelvic punctures only.

Thirty operators performed 267 operations.

One operator performed.....	44 operations
One operator performed.....	35 operations
One operator performed.....	27 operations
One operator performed.....	21 operations
One operator performed.....	15 operations
Two operators performed.....	14 operations (each)
One operator performed.....	12 operations
One operator performed.....	11 operations
One operator performed.....	10 operations
One operator performed.....	9 operations
One operator performed.....	8 operations
Two operators performed.....	6 operations (each)
One operator performed.....	5 operations
Four operators performed.....	4 operations (each)
One operator performed.....	3 operations
Six operators performed.....	2 operations (each)
Four operators performed.....	1 operation (each)

Anæsthesia.—In the large majority of these cases, nitrous oxide followed by ether, administered by the open drop method, has been used. Some patients have been given chloroform or ether only, and a few chloroform and ether.

DIAGNOSIS AT OPERATION

Ruptured with free blood in peritoneal cavity.....	100	} (61%)
Ruptured with encapsulated blood in peritoneal cavity.....	66	
Tubal abortion with free blood in peritoneal cavity.....	38	} (19%)
Tubal abortion with encapsulated blood in peritoneal cavity.....	13	
Unruptured.....	55	(20%)
Total.....	272	
Interstitial pregnancy, right.....	2 ¹	
Tubal pregnancy, right.....	135	
Tubal pregnancy, left.....	131	
Ovarian pregnancy, right.....	2 ²	
Total.....	270	

¹ Wynne, J. H. H. Bull. XXIX, No. 324, February, 1918.

² Cullen & McAll, Surg., Gyn. & Obst., 1912; Myer & Wynne, to be reported.

In one case the pregnant tube was ruptured during the examination under ether. Active hemorrhage at time of operation occurred in 20 cases.

The peritoneum was noted as blood stained before being opened in 43 cases.

The blood in the peritoneal cavity was designated as fluid in 66, clotted in 24 (infected, three); there were fluid and clots in 55 cases.

The opposite tube was noted to be normal in 15 cases.

The opposite ovary was noted to be normal in 12 cases.

The appendix was described as normal in 31 cases.

The appendix was involved in the sac in 11 cases.

The appendix was adherent to a myoma in one case.

A CASE OF PREGNANCY IN A RUDIMENTARY HORN

Gyn. No. 16727. The patient was a white woman, age 30, admitted to the hospital June 9, 1910, complaining of vaginal bleeding and pain the left side of the abdomen. Married five years; one child two years old. One miscarriage at two months, one year ago. Labor and puerperia normal. Last menstrual period January, 1910.

P. I.—The patient considered herself pregnant, but noticed that the uterus had not enlarged as rapidly as during her former pregnancy and that the enlargement was more on the left side than on the right. For a month she has noticed tenderness over the left side of the abdomen. At 6 a. m. on the morning of admission, she was awakened by pains in the pelvis, similar to labor pains and shortly after, passed blood and bits of tissue resembling placenta. There was slight bleeding afterwards, but the pain subsided. She was nauseated this morning.

Physical Examination Under Ether.—On abdominal examination, a mass can be felt in the lower abdomen, which is rather soft and boggy and about the size of a large orange. The mass is movable and seems to be attached to the uterus.

ADVANCED EXTRAUTERINE PREGNANCY

Gyn. No.	Race	Age of patient Years	Date	Pre-operative diagnosis	Operation	Placenta	Result	Fœtus
114	B.	29	1890	Fibrocystoma.	Laparotomy.	Removed.	Died. Shock.	Dead. Male. Length 53 cm.
191	B.	28	1890	Abdominal pregnancy (several mos. past term).	Laparotomy.	Removed.	Recovery.	Wt. 2800 grms. Male. Dead. Fully developed. Crown rump 30 cm.
1,795	W.	42	1893	Ectopic, two months past term.	Laparotomy.	Removed.	Died. General peritonitis.	Dead. Length, 42 cm.; wt., 4 lbs.
4,564	B.	45	1896	Calcified myoma or lithopedion four years past term.	Laparotomy.	Removed.	Recovery.	Lithopedion. Weight, 4½ lbs.
7,182	W.	34	1899	Multilocular cystoma ovarii.	(Reported by J. G. Clark). Laparotomy.	Removed.	Recovery.	Dead. Length, 25 cm.
12,207	W.	41	1905	Ruptured tubal pregnancy, two months past term.	Laparotomy.	Removed.	Recovery.	Macerated. Weight, 1250 grms. Dead.
13,272	B.	28	1906	Extrauterine pregnancy, ruptured.	Laparotomy.	Removed.	Recovery.	Full term, female. Living.
13,546	W.	35	1907	Extrauterine pregnancy, ruptured.	Laparotomy.	Removed.	Recovery.	Six months, 33 cm. long.
13,673	B.	30	1907	Abdominal pregnancy.	Laparotomy.	Removed.	Recovery.	Intraligamentary, full term.
13,806	B.	33	1907	Abdominal pregnancy. (Reported by Cullen, Surg., Gyn. & Obst., 1915, X, 261.)	Laparotomy.	Removed.	Recovery.	Macerated remains of fœtus.
17,656	W.	35	1911	Laparotomy.	Removed.	Recovery.	Dead. Intraligamentary, rt. Weight, 6½ lbs.
19,092	B.	22	1913	Extrauterine pregnancy, infected.	Laparotomy.	Removed.	Died. General peritonitis.	Macerated. Femur, 5.2 cm. Humerus, 4.8 cm.
21,494	B.	29	1915	Ovarian tumor, right.	Laparotomy.	Removed.	Recovery.	Dead. Weight, 1911 grms. 44.5 cm.

Pelvic Examination.—The vagina and cervix are normal. The fundus of the uterus is soft and boggy and, attached to it by a pedicle, is the mass described above.

Pre-Operative Diagnosis.—Extrauterine pregnancy or pregnancy in a rudimentary horn.

Operation.—The mass was found to be a pregnancy in the rudimentary left horn of a bicornate uterus and was attached to the right side of the uterus by a small pedicle. The left tube was stretched over the pregnant horn and together with the left ovary was so intimately associated with it as to necessitate their removal. The left horn was amputated close to the right side and there remained a practically normal uterus.

The patient was discharged on the 13th day after an uncomplicated convalescence.

Diagnosis.—Pregnancy in a rudimentary horn, left.

Pathological No. 15,150.—The specimen has been opened anteriorly in the operating-room and measures 7 x 8 x 5 centimeters. The walls measure 1.5 centimeter in thickness. Foetus of 4 to 5 months in unruptured membranes.

PATHOLOGICAL REPORTS

The tissues removed at operation have been studied histologically and the diagnosis has been verified. We are unable at the present time to give a thorough report on this interesting side of the disease.

The routine preparations, where the endometrium was examined, have been reported as follows:

Normal endometrium	13
Gland hypertrophy of the endometrium	5
Endometritis, chronic	5
Endometritis, acute	1
Decidual reaction of the endometrium	7
Cast of uterine cavity with decidual reaction	2

In addition to ectopic pregnancy the following diagnoses were made at or before operation:

Atrophy of the opposite tube	1
Hematosalpinx of the opposite tube	3
Hydrosalpinx of the opposite tube	16
Chronic salpingitis of the opposite tube	8
Pyosalpinx of the opposite tube	6
Tubo-ovarian abscess of opposite tube	1
Ovarian abscess	3
Chronic pelvic inflammatory disease	92
Cystic ovaries	13
Ovarian cyst, follicular	9
Ovarian cyst, corpus luteum	3
Parovarian cyst	1
Retroposition of the uterus	6
Myomata uteri	17
Membranous dysmenorrhea	1
Mesenteric cyst	1
General peritonitis	1
Pre-operative rupture of abscess into rectum	1
Post-operative adhesions	1
Bladder adhesions	1
Omental adhesions	14
Intestinal adhesions	19
Meckel's diverticulum	1

Umbilical hernia	2
Appendicitis, chronic	32
Appendicitis, sub-acute	5
Appendicitis, acute	2
Periappendicitis	7

Complications before operation:

Pulmonary tuberculosis	2
Diabetes	1
Insanity	1
Arthritis deformans	1
Chronic nephritis	1
Ascaris lumbricoides	1
Uncinaria Americana	1

POST-OPERATIVE COMPLICATIONS

The complications following operations have been as follows:

Acute bronchitis	2 cases with recovery.
Bronchopneumonia	2 cases with recovery.
Lobar pneumonia	2 cases with 1 death.
Fecal fistula, abdominal	2 cases with 1 death
Fecal fistula, vaginal	1 case with death...
Urinary fistula, abdominal	1 case with death...
Atonic ileus	1 case with recovery.
Peritonitis, general	6 cases with 5 deaths.
Infected drainage cavity with collection of pus	3 cases with recovery.
Cystitis	2 cases.
Phlebitis (of left leg)	3 cases.
Tetanus	1 case with recovery.
(Reported by Casler at Southern Medical Association meeting in 1917.)	
Gangrene of the hand following intra-arterial (radial) salt infusion	1 case.
Mastitis, right	1 case.
Acute follicular tonsillitis	1 case.
Influenza	1 case.
Erysipelas (facial)	1 case.

Shock and anemia have been omitted from this list, as accurate data for all cases are not available.

SUBSEQUENT OPERATIONS FOR COMPLICATIONS ARISING FROM THE PRIMARY OPERATION

Gyn. No. 2,612.	Abdominal drainage for peritonitis following rupture of sac by irrigation after pelvic puncture. Symptoms of peritonitis 11 days after operation. Recovery.
Gyn. No. 7,901.	Exploratory laparotomy for localized peritonitis 36 hours after left salpingo-oophorectomy and vaginal drainage. Death on the sixth day from lobar pneumonia.
Gyn. No. 11,473.	Pelvic puncture for drainage, 23 days after salpingo-oophorectomy. Recovery.
Gyn. No. 11,491.	Dilatation of drainage tract and evacuation of pus 10 days after pelvic puncture. Recovery.
Gyn. No. 12,380.	Rupture of abdominal incision 22 days after laparotomy. Recovery.
Gyn. No. 15,529.	Right salpingo-oophorectomy and release of adhesions 13 days after pelvic puncture and drainage of infected hematocoele. Recovery.

Gyn. No. 17,251. January 16, 1911, at the first operation, during hysterectomy, left salpingo-oophorectomy and release of adhesions, the rectum was torn. Abdominal fecal fistula resulted.

April 29, 1911. Excision of fistulous tracts, suture of rectum and bladder. Appendectomy. Failure.

September 18, 1911. The patient was readmitted to the hospital (Gyn. No. 17,804) for abdominal fecal fistula and a recto-vaginal fistula following her first operation.

September 30, 1911. Excision of abdominal fistula, resection of sigmoid, end-to-end anastomosis, suture of bladder. Shock.

October 5, 1911. Enterostomy for ileus.

October 6, 1911. Enterostomy for ileus. Death on the table.

CAUSE OF DEATH

There have been 13 deaths in our series of 303 cases and autopsies were performed on six of these.

Gyn. No. 114. (Autopsy No. 72.) Shock 12 hours after operation. This patient was in a very critical con-

dition when operated upon. No anatomical cause of death was found at autopsy.

Gyn. No. 521. (Autopsy No. 181.) Died 24 hours after operation. The anatomical diagnosis at autopsy was: Acute general peritonitis (pure culture *B. coli* from bloody peritoneal fluid), perforation of appendix with circumscribed abscess.

Gyn. No. 1,795. (Autopsy No. 388.) Died 10 days after operation. At autopsy an acute fibro-purulent peritonitis, chronic diffuse nephritis and gallstones were found.

Gyn. No. 7,901. (Autopsy No. 1562.) Death 6 days after operation, of lobar pneumonia.

Gyn. No. 10,678. (No autopsy.) Death 3 days after operation. On admission the hemoglobin was 15 per cent and on the day of death 10 per cent.

Gyn. No. 12,042. (No autopsy.) Death 9 hours after operation. This patient was operated on by the vaginal route and a large amount of clot and fluid blood evacuated, followed by a gush of bright red blood. Laparotomy was immediately performed. Shock.

TABLE SHOWING PREGNANCIES SINCE OPERATION

Gyn. No.	Character of operation	No. of years since operation	No. of children and miscarriages since operation
1,636	Incision of sac with drainage.....	24	5 full-term children.
1,710	Enucleation of sac.....	24	2 full-term children.
2,805	Right salpingo-oophorectomy.....	23	1 full-term child.
4,120	Pelvic puncture with drainage.....	20	2 full-term children.
6,482	Right salpingectomy.....	17	1 miscarriage at 2½ months 4 years after operation.
8,441	Right salpingo-oophorectomy.....	15	2 full-term children, 1 miscarriage.
9,740	Left salpingectomy.....	14	1 miscarriage.
9,746	Right salpingo-oophorectomy.....	14	5 miscarriages, the first 2 years after operation.
10,258	Left salpingectomy.....	14	1 full-term child.
10,544	Left salpingectomy with resection of right ovary.....	14	2 full-term children.
11,215	Right salpingo-oophorectomy.....	13	2 full-term children.
11,244	Pelvic puncture and exploratory laparotomy.....	13	1 full-term child.
11,592	Right salpingectomy.....	13	6 full-term children.
11,830	Pelvic puncture.....	12	1 tubal pregnancy 8 years after operation.
11,834	Left salpingo-oophorectomy.....	12	1 full-term child.
12,236	Right salpingo-oophorectomy.....	12	2 miscarriages 10 and 8 years ago at 3 months; 1 full-term child 6 years ago.
12,268	Right salpingectomy.....	12	1 miscarriage.
12,398	Right salpingo-oophorectomy.....	12	2 miscarriages.
14,167	Left salpingo-oophorectomy and resection of right ovary..	10	1 full-term child.
15,309	Left salpingo-oophorectomy.....	8	1 full-term child 2 years after operation; 1 miscarriage 6 years after operation.
15,644	Right salpingo-oophorectomy.....	8	1 miscarriage and 1 full-term child 3 years after operation.
15,955	Left salpingo-oophorectomy.....	7	1 full-term child.
17,428	Right salpingectomy.....	5	1 full-term child.
18,744	Right salpingectomy.....	4	1 full-term child 14 months after operation; 1 full-term child 32 months after operation.
19,781	Right salpingectomy.....	3	8 months pregnant when heard from.
20,777	Resection of right cornu.....	2	1 full-term child 1½ years after operation.
21,017	Right salpingectomy, resection of right ovary, myomectomy.	2	1 full-term child 1 year after operation.
21,082	Right salpingectomy.....	23 months	1 miscarriage (induced) 6 months after operation.
21,483	Right salpingectomy.....	20 months	3 weeks from term when heard from.
22,303	Right oophorectomy.....	18 months	1 full-term child 18 months after operation.
22,445	Left salpingo-oophorectomy.....	16 months	1 full-term child 11 months after operation.

FIVE PATIENTS OPERATED ON FOR SECOND ECTOPIC PREGNANCY IN THIS CLINIC

Gyn. No.	First operation	Second operation	Gyn. No.
4,147	Pelvic puncture in 1896.....	Right salpingectomy in 1904.....	11,590
9,781	Right salpingo-oophorectomy in 1902.....	Left salpingo-oophorectomy in 1905.....	12,290
13,776	Left salpingectomy in 1907.....	Right salpingectomy in 1908.....	14,895
15,771	Right salpingectomy in May, 1909.....	Left salpingectomy in November, 1909.....	16,188
16,230	Right salpingo-oophorectomy in November, 1909.....	Hysterectomy; left salpingo-oophorectomy in January, 1911.....	17,251

These six fatalities were reported in Kelly's Operative Gynecology, Vol. II.

Gyn. No. 12,830½. (No autopsy.) Death 4 hours after operation. The patient was in serious shock when operated upon. About 2 liters of free blood were evacuated from the abdomen.

Gyn. No. 15,314. (No autopsy.) Death 3 days after operation from shock. (Reported by E. H. Richardson.)

Gyn. No. 17,119. (No autopsy.) Death 2½ hours after operation. The patient was in good condition after the operation until 3 minutes before death. Probably embolus.

Gyn. No. 17,211. (Autopsy No. 3489.) Death 8 days after operation. Anatomical diagnosis at autopsy: Acute general peritonitis.

Gyn. No. 17,251. (No autopsy.) Death 8 days after secondary operation for fistula following primary operation. General peritonitis.

Gyn. No. 18,731. (No autopsy.) Death 2½ hours after operation. Shock. This patient had diabetes.

Gyn. No. 19,092. (Autopsy No. 3884.) Death 12 days after operation. At autopsy acute general peritonitis and embolic pneumonia were found. At operation the sac containing fetal bones and infected material was ruptured.

IMMEDIATE RESULTS

Well	271 (89.4%)
Improved	19 (6.3%)
Died	13 (4.3%)

ULTIMATE RESULTS

Letters were sent to the 290 patients who recovered from the operations for ectopic pregnancy. Answers to the fol-

low-up letters were obtained from 118 patients and nine, who did not answer the letter, were later readmitted to this hospital. Of 120 patients, 100 have been well since operation, five have had poor health since operation, seven report fair health and two no change in general health since operation. Four had good health for several months or years, and afterwards died, one of pulmonary tuberculosis, one of acute intestinal obstruction, one of post-operative pneumonia. In one case the cause of death was not stated.

Of the series of 127 cases, there was no possibility of future pregnancy in 33. Of the remaining 96 in whom there was a possibility of future pregnancy 36 (38%) have since become pregnant one or more times; 61 pregnancies have resulted in 37 full-term children; two patients were pregnant almost at term when heard from. In 16 cases the pregnancy ended in miscarriages and six patients had a second extrauterine pregnancy.

OPERATIONS SUBSEQUENT TO OPERATION FOR ECTOPIC PREGNANCY

Post-operative ventral hernia has occurred in eight cases; four have been repaired in this hospital and one in another hospital, and three patients have not been submitted to another operation. One patient was operated upon for intestinal obstruction and one had a vaginal panhysterectomy performed in this hospital for carcinoma of the cervix.

In all 145 patients have been followed on this point.

I wish to thank Dr. Howard A. Kelly for permission to publish this report.

NOTES AND NEWS

Dr. George Blumer is Chairman of the Medical Advisory Board, Yale University, New Haven, Conn.

Dr. Montague Boyd is Associate Professor of Surgery (Genito-Urinary), Emory University; Andrologist, Wesley Memorial Hospital and Visiting Genito-Urinary Surgeon, Grady Hospital, Atlanta, Ga. Government service: Captain, M. R. C., on duty in France.

Dr. Walter V. Brem is Major M. C., and Chief of the Medical Service, U. S. Army Base Hospital, Camp Fremont, Cal.

Dr. Helen Smith Brown is Lecturer in Social Hygiene for the Commission on Training Camp Activities, Washington, D. C.

Dr. S. W. Clausen is Instructor in Pediatrics, Washington University Medical School and Assistant Physician to the St. Louis Children's Hospital. He is First Lieutenant, M. R. C., and is in active service.

Dr. Malvern B. Clopton is Major, M. R. C. He is a member of Washington University Hospital Unit No. 21, and is stationed with General Hospital No. 12, B. E. F., Rouen, France.

Dr. Stanley Cobb is First Lieutenant, M. C., Division of Brain Surgery.

Dr. Sydney M. Cone is Captain, M. R. C., and is stationed at the Alder Hey English Military Orthopedic Hospital, England.

Dr. Henry Wireman Cook is Associate Director of the Bureau of Medical Service, American Red Cross, Washington, D. C.

Dr. W. L. Cousins is Surgeon-in-Chief of St. Barnabas Hospital, Portland, Me. Government service: Major, M. R. C., and Chief of the Surgical Staff U. S. Army Base Hospital, Camp Gordon, Ga.

Dr. J. Staige Davis is Captain, M. C., U. S. Army, and is on active duty in Baltimore.

Dr. Ernest C. Dickson is Associate Professor of Medicine, Leland Stanford University School of Medicine. Government service: Captain, C. A. M. C., stationed in Basingstoke, England.

Dr. Richard N. Duffy is Surgeon to the New Bern General Hospital, New Bern, N. C.

Dr. C. B. Dunn is Chief of Staff, Southeastern Hospital for the Insane, Madison, Ind., and on the teaching staff King's Daughters Hospital, Madison, Ind.

Dr. Arthur B. Emmons is Captain, M. R. C., and is stationed in Evacuation Hospital No. 2, A. E. F., France.

Dr. W. L. Estes, Jr., is Director of St. Luke's Hospital, South Bethlehem, Pa. Government service: Captain, M. R. C., attached to Mobile Operating Unit No. 1, Section No. 1, A. E. F., France.

Dr. William W. Farr is Captain, Medical Corps, U. S. A., stationed at U. S. Base Hospital, Camp Shelby, Hattiesburg, Miss., with title of Chief of Subsection of Otolaryngology.

Dr. A. L. Fisher is Captain, M. C., and is in charge of the Surgical Service, U. S. Base Hospital No. 30, A. E. F.

Dr. J. M. T. Finney is Brigadier General, M. C., U. S. Army, and is Surgical Consultant, A. E. F., France.

Dr. Simon Flexner is Lieutenant Colonel, Medical Corps, U. S. A. He is on duty at the Rockefeller War Demonstration Hospital, New York City.

Dr. James R. Garber is Instructor in Obstetrics South Highlands Infirmary Training School for Nurses, Visiting Obstetrician to the Hillman Hospital, Attending Obstetrician to the Salvation Army Home, Birmingham, Ala., and Acting Secretary of the Southern Medical Association.

Dr. S. McPheeters Glasgow is Captain, M. C., and is stationed at Camp Zachary Taylor, Ky.

Dr. L. W. Gorham is Captain, M. R. C., and is stationed with U. S. Base Hospital No. 33, Portsmouth, England.

Dr. F. F. Gundrum is Vice-President, California State Board of Health, and Consulting Physician, Sacramento County Hospital. Government service: Chairman Medical Advisory Board No. 7, Sacramento, Cal.

Dr. Louis Hamman is Acting Physician-in-Chief to The Johns Hopkins Hospital and Acting Professor of Medicine, Johns Hopkins University.

Dr. F. M. Hanes is connected with Base Hospital No. 65, A. E. F., France.

Dr. Henry Harris is Instructor in Medicine, University of California. Government service: Member of Medical Advisory Board, District No. 5, California.

Dr. R. F. Hegeman is Captain, M. R. C., and is Assistant Chief of Base Hospital No. 96.

Dr. Campbell P. Howard is Professor of Theory and Practice of Medicine and Clinical Medicine, State University of Iowa, and Physician to the University Hospital.

Dr. Henry T. Hutchins is Major, M. C., and is Surgeon-in-Chief, Evacuation Hospital No. 49, A. E. F.

Dr. J. Edwards Kerney is Visiting Urologist, Memorial Hospital, Pawtucket, R. I.; Visiting Urologist to Rhode Island State institutions; Associate Visiting Urologist to St. Joseph's Hospital, Providence, R. I.; and Surgeon in Urology to Rhode Island Hospital, O. P. D., Providence, R. I.

Dr. Clarence F. M. Leidy is Captain, M. C., 62d Pioneer Infantry, Camp Wadsworth, S. C.

Dr. Hans Lissner is Instructor in Medicine, University of California Medical School, and Assistant Visiting Physician, University of California Hospital. Government service: Chief Examining Physician, Local Draft Board No. 4, Oakland, Cal.

Dr. Herbert M. Little has taken up again his work as Assistant Professor of Obstetrics and Lecturer in Gynecology, McGill University, after two years' duty overseas with the Canadian Army Medical Corps. He is also Assistant Attending Obstetrician, Montreal Maternity, and Assistant Attending Gynecologist, Montreal General Hospital.

Dr. David Russell Lyman is Medical Superintendent, Gaylord Farm Sanitarium, and Clinical Lecturer on Tuberculosis, Yale Medical School. He was for six months with the Rockefeller Commission for the Prevention of Tuberculosis in France, and with the Tuberculosis Bureau of the American Red Cross.

Dr. W. G. MacCallum is Contract Surgeon, U. S. Army.

Dr. J. D. Madison is Captain, M. C., and is stationed in Milwaukee, Wis., as President of the Examining Board for Medical Officers' Training Camp, etc.

Dr. W. McK. Marriott is Professor of Pediatrics, Washington University Medical School, Physician-in-Chief to the St. Louis Children's Hospital, and Consulting Physician to the St. Louis City Hospital and the St. Louis Isolation Hospital.

Dr. Robert T. Miller is Lieutenant Colonel, M. C., Director U. S. Base Hospital No. 27, and Chief of Surgical Staff Mobile Hospital No. 1.

Dr. Ralph G. Mills, Assistant Resident Pathologist Johns Hopkins Hospital, is Professor and Head of Department of Pathology, Peking Union Medical College, Peking, China (absent on leave).

Dr. George R. Minot, Jr., is Assistant Professor of Medicine, Harvard Medical School; Associate in Medicine, Massachusetts General Hospital, and Assistant Consulting Physician to Collis P. Huntington Memorial Hospital of the Harvard Cancer Commission.

Dr. Roger S. Morris is Forchheimer Professor of Medicine, Medical Department University of Cincinnati; Director of the Medical Division Cincinnati General Hospital, and Director of the Outdoor Dispensary. Government service: Major, M. C., on duty abroad.

Dr. W. Bean Moulton is Captain, M. R. C., and is stationed at Camp Greenleaf, Chickamauga Park, Ga.

Dr. C. D. Parfitt is Lecturer on Medicine, University of Toronto, and Advisor to the Tuberculosis Clinic, General Hospital, Toronto.

Dr. Francis W. Peabody is Assistant Professor of Medicine, Harvard Medical School; Physician to the Peter Bent Brigham Hospital, and Consulting Physician to the Collis P. Huntington Memorial Hospital. Government service: Major, M. C., on active duty in France.

Dr. Louise Pearce is Associate in Pathology at the Rockefeller Institute for Medical Research, New York City.

Dr. Clement A. Penrose is Major, M. R. C., at present on inactive duty.

Dr. H. W. Plaggenmeyer is Captain, M. C., and is on active duty in France.

Dr. Alexander Randall is Captain, M. R. C., and is stationed with the 6th Army Corps, France.

Dr. George K. Rhodes is First Lieutenant, Medical Corps, U. S. A., on duty at U. S. Base Hospital, Camp Meade, Md.

Dr. Hunter Robb is Major, M. R. C. He is stationed in the Medical Officers' Training Camp at Camp Greenleaf, Ga.

Dr. Peyton Rous is Associate Member, Rockefeller Institute for Medical Research, New York City, and Vice-Chairman, Division of Medicine and Related Sciences, National Research Council, Washington, D. C.

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FLUOROSCOPY OF THE CEREBRAL VENTRICLES

By WALTER E. DANDY

(From the Department of Surgery, The Johns Hopkins Hospital and University.)

In a recent communication,¹ it was shown that if air is substituted for the cerebrospinal fluid in the ventricles of the brain, an accurate outline of the lateral ventricles will be cast in a roentgenogram. This offspring of radiography, which we have called pneumoventriculography or ventriculography, has already proved of great value in the diagnosis and localization of many intracranial lesions which without its aid would either have been overlooked or incorrectly localized.

Heretofore, shadows have been produced in the gastro-intestinal and genito-urinary tracts and elsewhere by the introduction of solutions or suspensions offering a particular resistance to the penetration of the X-rays. The injection of any such media into the ventricles of the brain is, however, absolutely precluded on account of injury to the brain and because their elimination is impossible; and even if it were permissible to inject them into the ventricles, the specified substances would not yield shadows so striking as those obtained in abdominal work.

The distinctness of an X-ray shadow is emphasized by contrast. The abdominal wall, composed of soft, easily penetrable and light shadow-casting tissues, emphasizes the dense shadows cast by resistant media.

The skull shadow is, however, so dense that it would subdue the outlines of shadows cast by any resistant fluid media which might be injected into the ventricles. Against a background of skull and brain shadow, the air-filled ventricle is

sharply outlined. Air has proven so satisfactory in every way that we have as yet seen no need of substituting other gases for it, though it is possible that a gas, such as hydrogen (with the lowest density), might produce an even more distinct shadow.

Recently, at the suggestion of Dr. J. William Pierson, these X-ray studies have been amplified by observations under the fluoroscope. The results have been equally striking. The ventricles are outlined just as distinctly as in the X-ray plate. From a series of over 75 cases from Professor Halsted's clinic, in which air has been introduced into the ventricles, 20 have had fluoroscopic studies in addition to the X-ray plates. The ages of the patients examined under the fluoroscope have ranged from three months to 55 years. The ventricles were almost as distinct in adults as in infants and young children, though stronger rays were necessary to penetrate the thicker skulls. The size of the ventricles has ranged from normal to the extreme grades of dilation in advanced hydrocephalus. From 20 to 350 c. c. of air have been introduced into the ventricles.

Just as in fluoroscopic and X-ray studies elsewhere, each method has certain advantages not possessed by the other. The value of each is in large part supplementary, and the best results are therefore obtained by combining the salient advan-

¹Dandy, W. E. Ventriculography Following the Injection of Air into the Cerebral Ventricles. *Ann. Surg.*, July 1918.

tages of each. A fluoroscopic study of the cerebral ventricles yields the same results as a series of ventriculograms. Either profile or anteroposterior views of any part of one or both lateral ventricles can be obtained under the fluoroscope at will by the proper movement of the head. Every part of both lateral ventricles can be systematically observed during a single examination. In this way, the result will be a composite picture of the ventricular system. Fluoroscopic studies, however, lack the graphic and permanent record of the ventriculogram. The interpretations at a fluoroscopic examination are necessarily dependent upon transient and hasty impressions which make the personal equation too prominent in questions of doubt, particularly when the observer's experience is limited, and especially at the present time when at best our knowledge of the normal and the pathological is uncertain.

The technique of the air injection has been described elsewhere. In over 75 cases no deleterious results have occurred. At times slight symptoms of intracranial pressure develop, but quickly subside on release of the air by ventricular puncture.

PROCEDURE FOR FLUOROSCOPIC EXAMINATION

Fluoroscopic rays passing through a normal or a hydrocephalic head show nothing to the observer except a homogeneous dark mass of the head, with slight accentuation of the bony landmarks. There is not sufficient difference between the density of cerebrospinal fluid and normal or pathological cerebral tissue to make any differential impression on the rays, regardless of the proportion of these constituents. When air is injected into the ventricles the reduction in density is so great that the ventricles stand out as a clear zone in strong relief against this dark background. The contrast is almost as striking as that seen under the fluoroscope when bismuth or barium is introduced into the stomach.

The usual fluoroscopic equipment contains a separate apparatus for vertical and horizontal rays. When the vertical rays are used, the patient is placed in the recumbent position. When horizontal rays are used, the patient must be sitting or standing. *For ventricular fluoroscopy the vertical rays and the recumbent position yield the most important results.* Horizontal rays and the sitting posture are less satisfactory because the dependent part of the ventricle contains fluid, this giving the ventricle a horizontal bisected appearance (Fig. 4). Only the upper part of the ventricle is then visible. When the patient is recumbent and the head is on the side, a full profile view of one ventricle is obtained because all the fluid has passed to the dependent ventricle.

The horizontal rays, utilizing the sitting posture, are very useful to demonstrate the movements of air in the ventricle and to understand the necessary positions to be assumed in shifting air from one terminus of the ventricular system to the other. When the head is at rest in this position, a line of demarcation is evident at the dividing line between fluid and air (Fig. 3). Each movement of the head temporarily disturbs this fluid level, which quickly reforms with rest, just as in hydropneumothorax. Since only part of the fluid in the

ventricles is usually replaced by air, it is evident that the position of the head will determine the part of the ventricular system that will contain air or fluid at a given time. The movement of air and fluid in hydropneumothorax is simple, because there is a single large cavity. To move the air from one part to another of the ventricular system is more difficult owing to the curves, angles and branches of the lateral ventricles and to the points of narrowing at the foramina. Moreover, since the lateral ventricles are paired and communicate only anteriorly through the small foramina of Monro, these difficulties become greater. Beginning with a small amount of air in the descending horn of one lateral ventricle, by changing the position of the head one can observe the air passing into the posterior horn, then the body, the anterior horn, through the foramen of Monro into the third ventricle. From the third ventricle it passes through the opposite foramen of Monro into the opposite lateral ventricle and by reversing the movements of the head the air may be sent to the descending horn of this ventricle. The necessary movements are best understood by visualizing the ventricular system in three dimensions. Needless to say, since air is lighter than fluid, its movement in the ventricle is in the direction opposite to the movement of the head, or the reverse of gravity of fluid.

The rapidity of transfer of fluid from one lateral ventricle to the other varies with the size of the foramina of Monro. In advanced hydrocephalus much additional communication between the lateral ventricles results from large perforations in the septum lucidum due to absorption from increased intraventricular pressure. Up to a certain stage the size of the foramina of Monro is proportionate to the size of the ventricles. After additional communication following rupture of the septum lucidum, increase in size of the foramina of Monro ceases. In normal or slightly enlarged ventricles the air passes from one lateral ventricle to the other only when the position of the head is such (occiput down) that all the air is in the anterior horn. If the head is then turned toward the side containing the air, air passes through the interventricular foramina to the opposite lateral ventricle. When the interventricular septum is destroyed, the air rushes rapidly through these artificial openings from one lateral ventricle to the other without regard to the anteroposterior position of the head. This can be observed under the fluoroscope in the anteroposterior view either with the vertical or horizontal rays.

In normal or moderately enlarged ventricles there is an uneven distribution of air in the two lateral ventricles when viewed anteroposteriorly. Only in large ventricles with very large foramina of Monro or in which there are artificial openings in the septum lucidum, is the communication between the lateral ventricles ample to give an equal distribution of air on the two sides without careful manipulations of the head. In a lateral view, with the patient sitting, two superimposed levels of air and fluid—one for each ventricle—can be seen when the head is tilted to one side. In advanced hydrocephalus, the two cavities are practically fused into a single space, so that the fluid in the two sides quickly assumes the same level.



FIG. 1.—Drawing by Miss Norris to show the fluoroscopic picture of a lateral ventricle in a case of advanced hydrocephalus. Note the false ventricular hernia caused by a local rupture of the thinned cortex over the anterior fontanelle (Fig. 9). The diagnosis of hydrocephalus and of the direct connection of the swelling with a lateral ventricle were made only by the fluoroscope and pneumoventriculography.

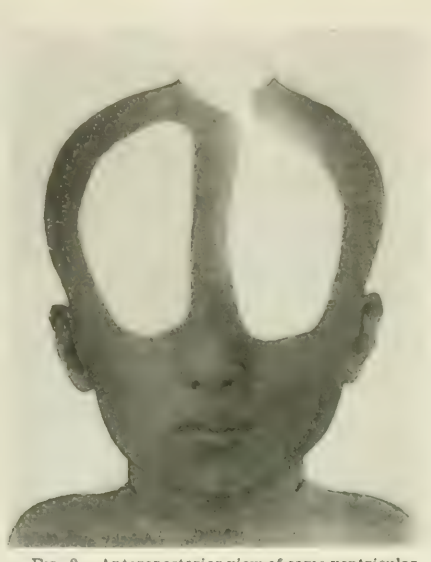


FIG. 2.—Anteroposterior view of same ventricular hernia. The sac communicates with only one lateral ventricle. The degree of enlargement of the ventricles can be accurately determined from this view. Figs. 1 and 2 are viewed in the recumbent posture and therefore vertical rays are used.



FIG. 3.—Profile view of lateral ventricle of same case (Figs. 1 and 2), but the patient is sitting and horizontal rays are used. The lower part of the ventricle does not show, because in this posture it is filled with fluid (due to gravity). Note the sharp horizontal line of demarcation at the fluid-air level. The ventricular hernia shows as well as in the previous figures because it is uppermost.



FIG. 4.—Same as Fig. 3 except head is tilted slightly to one side, thus showing the two levels of fluid (A and B); one fluid level for each lateral ventricle. In ventricles as large as these the communication between the two lateral ventricles is so free, through the foramen of Monro and the septum lucidum, that these two levels of fluid are only transient. The levels soon merge regardless of the anteroposterior position. In smaller ventricles the two levels remain, but of course are superimposed when the position of the head is exactly vertical.



FIG. 5.—Showing the transfer of air to anterior part of lateral ventricles when the head is bent backward. The horizontal fluid level remains in all cases in which horizontal rays and vertical positions are used.

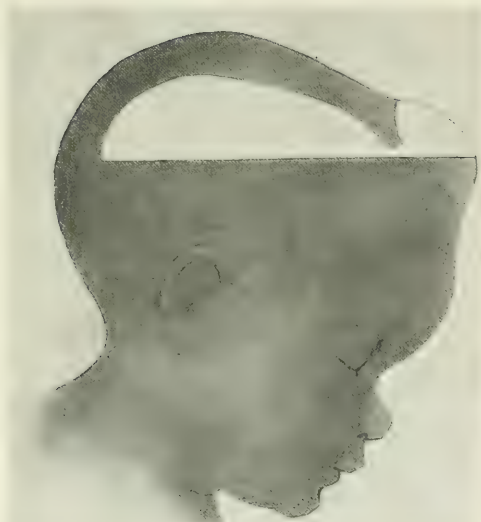


FIG. 6.—To show distribution of fluid when the head is bent forward. Note that most of the air is now in the posterior part of the lateral ventricle, but the fluid level is such that the sac and the neck of the sac are partly filled with air. With a little more tilting of the head forward, the sac would contain only fluid.



FIG. 7.—Anteroposterior view. Showing transfer of fluid from one lateral ventricle to the other. When the head is tilted to one side, the amount of air which crosses depends entirely upon the angle assumed. When the head is bent to a horizontal line all the air will be in the upper ventricle.

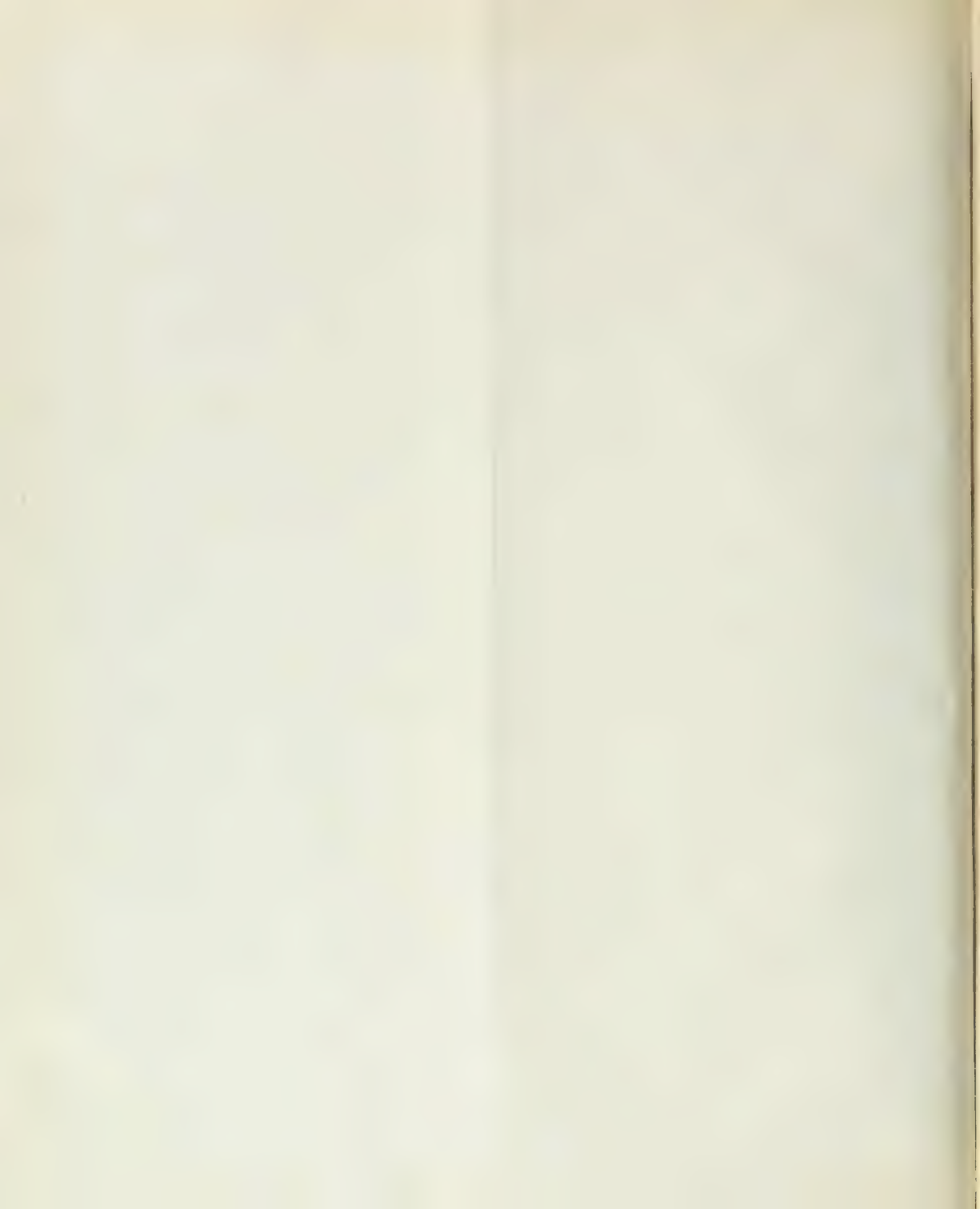


FIG. 8.—Photographs of child with swelling over anterior fontanelle. The black lines mark the limits of the fontanelle.



FIG. 9.—(A) View from above of brain from which preceding fluoroscopic studies were made. Note the rupture in the cortex through which the cerebrospinal fluid passed into the swelling in the scalp. The fluid remained localized owing to the adhesions which formed around the opening.

(B) Section of same brain to show size of lateral ventricles. Despite the great size of ventricles the head was only slightly enlarged.



PRACTICAL RESULTS FOLLOWING FLUOROSCOPY

In this series of cases the results from fluoroscopic study have been practically the same as from ventriculography. Many cases of hydrocephalus have been studied with or without other complicating conditions. Either by ventriculography or fluoroscopy the dilated ventricles are pathognomonic. In many cases a positive diagnosis could not have been made in any other way. In several cases the ventricles were normal or nearly so.

A very interesting case was reported to me by Dr. Blackfan from Professor Howland's clinic. A child five months old was brought into the hospital because of a lump over the anterior fontanelle. The swelling was about as large as a walnut, was soft and fluctuant. It was situated just to the left of the midline. The head was slightly large and the anterior fontanelle wider than normal. The diagnosis of meningocele seemed most probable. A fluoroscopic study with air in the ventricles at once made an unusual diagnosis clear. The interior of the swelling was in direct continuity with a lateral ventricle. The air could be made to enter or depart at will by suitable manipulations of the head. In the anteroposterior views this swelling could be seen to connect with one ventricle only. In addition to the ventriculocele, or false ventricular hernia, was an advanced hydrocephalus, suspected, but demonstrated only by fluoroscopy or ventriculography. At necropsy the findings were substantiated. Following a local area of atrophy in the cortex, the ventricular wall had ruptured and the fluid had become encapsulated by being walled off in the scalp. In the accompanying figures (Figs. 1 to 7) this case has been used to demonstrate the movements of air in the ventricles resulting from change of position of the head.

A second patient was a boy of 12, blind from intracranial pressure. The diagnosis could not be agreed upon. Cerebellar tumor with obstructive hydrocephalus, oxycephalus, and communicating hydrocephalus were the final divergent diagnoses reached. A discussion of the differential diagnosis would be irrelevant here, except to indicate that by fluoroscopy of the ventricles and by ventriculography an advanced hydrocephalus was demonstrated. This excluded so-called oxycephalus. Though hydrocephalus had been proven, the differential diagnosis between the obstructive and communicating types of hydrocephalus cannot at present be made positively either by ventriculography or fluoroscopy. A cerebellar exploration failed to disclose a tumor. The phenolsulphonophthalein test excluded tumor and made an absolute diagnosis of communicating hydrocephalus.

In a third case hydrocephalus was diagnosed by fluoroscopy, in a child five days old, with a normal-sized head. Hydrocephalus was suspected by Dr. J. Whitridge Williams at birth because the fontanelles were wide. A lumbar meningocele with paraplegia was also suggestive. By fluoroscopy a well-advanced dilation of the ventricles was demonstrated.

In a fourth case a transcortical operation had been made into the lateral ventricle some time previously. In the fluoroscopy the operative defect could be observed as a pouch from the already dilated ventricle. A fifth case had an advanced grade of hydrocephalus. The diagnosis was evident from the enlarged head, so that fluoroscopy was of interest more than of practical value. The large head was almost entirely filled with fluid; the septum lucidum was destroyed so that the two lateral ventricles were practically a single cavity with little indication of their former shape. In three cases recovering from meningitis hydrocephalus was diagnosed by the moderate ventricular enlargement which was visible under the fluoroscope. In none of these was hydrocephalus suspected, though the lethargy and stupor of the children indicated some intracranial complication.

Fluoroscopy has as yet been employed only in a limited number of conditions. Several times we have seen air in the cisterna magna indicating the patency of all the ventricular foramina but have not yet observed its passage through the aqueduct of Sylvius and fourth ventricle. It should be possible to demonstrate dislocation or partial obliteration of one or both ventricles from tumor pressure and thus help to localize the tumor. The rare cases of unilateral hydrocephalus with occlusion of the foramen of Monro should also be diagnosed by the unilateral ventricular dilatation and by the absence of communication between the ventricles of the two hemispheres. In this condition the difference in size of the two ventricles could be determined only by making a separate injection of air into each lateral ventricle.

The normal-sized ventricles have been observed in an adult and two children. Aside from the difference in size of the ventricles the air passes from one side to the other much more slowly, and more careful manipulations of the head are necessary to accomplish the transfer.

CONCLUSIONS

1. The lateral cerebral ventricles, when filled with air, can be clearly seen under the fluoroscope: 25 cases have been studied by this method.
2. The results in adults are equally as good as in children.
3. By fluoroscopy hydrocephalus can be accurately diagnosed at all stages of its development.
4. Several unsuspected cases of hydrocephalus have been demonstrated by the fluoroscope.
5. The diagnosis of a false ventricular hernia (ventriculocele) was made with certainty, because the air from the ventricle could be seen to pass directly into the swelling.
6. Fluoroscopy of the ventricles has practically the same range of utility as ventriculography, and almost the same results have been obtained. Following the injection of air into the ventricles, both fluoroscopy and ventriculography should be used.

STEREOROENTGENOGRAMS OF THE INJECTED LUNG AS AN AID TO THE STUDY OF THE LUNG ARCHITECTURE

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In a previous communication I have given the general directions for the preparation of a differential injection mass which is especially applicable to the study of the distribution of the blood-vessels within the lung by means of stereoroentgenograms, for it clearly brings out their relation to the bronchi, to each other, and to the lobation of the lung. The basis of the injection mass consists of a suspension of corn-starch in 70 per cent alcohol, to which vermilion granules are added when it is desired to obtain a uniform dense shadow, and ultramarine blue granules when a less dense and finely granular shadow is desired as a differential injection mass. By the use of a greater or less quantity of the 70 per cent alcohol the injection masses may be made to penetrate to any desired distance within the lung. If the bronchi alone are to be injected a thick vermilion mass gives the best results; for if the mass be too thin it will penetrate the air sacs and a blurred shadow will result, or else the whole lung will appear solid.

The relation of the pulmonary artery, the pulmonary vein, and the bronchi to each other can be summarized as follows: The pulmonary artery follows in all of its subdivisions the subdivisions of the bronchial tree. As each main branch of the pulmonary artery arches over its corresponding stem bronchus it comes to occupy a position posterior (dorsal) and slightly lateral to the bronchus. The relation of the main trunks of the pulmonary vein to the bronchi is quite different; they are situated anterior (ventral) and mesial to their stem bronchi and in their ultimate distribution are situated as far removed from the bronchi as possible. I lay emphasis on "as possible" for in some situations they are found near the bronchi, but never as closely associated with it as in the artery. In one of the illustrations frequently used to show the relation of the pulmonary artery to the stem bronchi (that of Aeby) the position of the artery is correctly shown in the right lung, but in the left lung the position is reversed. The diagram given by Merkel is correct.

Keeping these relations in mind let us consider some of the practical applications of these injection masses to the anatomy of the lung, and for this purpose the lung of the pig and of the dog will be used. In Stereo 1, we have a stereoroentgenogram of the lung of a pig in which the pulmonary artery was injected with the vermilion starch mass and then distended with air. The heart has been removed and the free portion of the artery has been reflected anteriorly in order that the cannula and its clamp may not interfere with a clear picture of the bifurcation of the trachea and the main venous trunks which pass to the lower lobes of the lung. We recognize at once the dense shadow caused by the injected artery and we can follow its ramifications until they are lost just beneath the pleura. Lying on the

mesial side of the artery in each lung we can recognize a hollow tube which, as we trace it anteriorly, joins its fellow and forms the trachea; these are the main stem bronchi. Situated on the mesial side of each bronchus, a third shadow, a trifle denser than the air-distended bronchi, can be seen; this is the main stem of the pulmonary vein. Because the artery has been filled with a distending injection it is pushed more to the lateral side of the bronchus than normal, and therefore throughout the greater part of its course appears to be situated at one side of the bronchus. It is, however, more closely applied to the bronchus than the vein, which shows an appreciable space between it and the bronchus throughout its entire course. The angle at which these three vessels enter the hilum of the lung differs on the two sides; on the right side the bronchus and artery enter the hilum pulmonis at a more acute angle than on the left side. The interweaving of the artery, bronchus, and vein which shows so distinctly in the lobus medius and the lobus superior of the right lung and in the lobus superior of the left lung is quite different from the hazy, smoky areas which are present in the early stages of tuberculosis.

In Stereo 2, we have a stereoroentgenogram of the lung of a pig in which the pulmonary vein of the left lobus inferior was partially injected with a thick ultramarine blue starch mass and then distended with air. The pulmonary vein can be clearly seen situated anterior and mesial to the main stem bronchus. This relation, to one who is not familiar with the architecture of the lung, is not so apparent in the preceding stereo. The pulmonary artery, because of its position and because it is uninjected, is not easily recognized; but if the walls of the stem bronchi, especially that of the right lobus inferior, be closely studied, it will be seen that the lateral wall is denser than the mesial wall, and if this density be followed forward it will be found to be the continuation of the main trunk of the pulmonary artery, which can be seen just beneath the point where the glass cannula which is inserted into the pulmonary vein is connected with the short piece of rubber tubing. The second ventral branch of the stem bronchus in the left lobus inferior also shows in a characteristic manner the same increased density. In the left lobus superior it is the conformation of the lobe and a thin sheet of connective tissue that occasion the apparent thickening of the lobus. This increased density of the lateral wall of the bronchus is frequently seen in stereos of the human lung, when from any cause (heart lesion) there is unusual distention of the pulmonary artery. In like manner, any lesion causing distention of the pulmonary vein may occasion an increased density of the mesial wall of the stem bronchus.

The thesis has already been advanced that the bronchus and artery are closely related to each other, while the vein is as far removed from the bronchus as possible. In the left lobus inferior when the course of the veins is in a horizontal plane there can be seen, between the injected veins, less dense shadows. As these are followed towards the midline they are found to join the stem bronchus; these densities are occasioned by the lateral branches of the stem bronchus. We find, then, a vein between two bronchi or, better, a bronchus between two veins. As these branches are followed through all parts of the lobe the veins appear to change their relation to the bronchi. This is due to the natural curvature of the lung, a fact that is sometimes overlooked in studying roentgenograms of the lung.

In the middle zone (third) of the lobus inferior of the right lung there can be seen scattered along the bronchi circular areas which show increased density. These are usually explained as being occasioned by a bronchus of the third or fourth order extending directly towards or away from the observer. If these densities be carefully examined they will be found to be of larger size than adjoining bronchi and often irregular in their contour. That these densities are due to bronchi alone may be true in some instances; that in the majority of instances they are occasioned by cartilages of peculiar form, which may or may not show a small amount of calcification, will be brought out in a forthcoming publication by the author. These circular densities are not always seen in a horizontal plane, but, as for example in the right lobus superior, they may have an oblique position as regards the observer. Scattered along the right stem bronchus, densities, due to the supporting cartilages, can be recognized in the angle between the stem bronchus and its branches. With a little study these densities can be differentiated from that due to the pulmonary artery.

In Stereo 3, we have a stereoroentgenogram of the lung of a dog in which the pulmonary artery was injected with a vermilion starch mass and the pulmonary vein with an ultramarine blue starch mass. The uniform dense shadow is the artery; the less dense and finely granular shadow is the vein. The bronchi do not show, being obscured by the injection of

both the artery and vein. The lung is rotated slightly to the right and the heart is displaced forwards in order that the main blood-vessels can be clearly seen. This brings the left pulmonary artery into a prominent position in the upper part of the stereo. The small artery clamp was used to close a leak which prevented the lung from being fully distended.

In studying this stereo it should be kept in mind that the position of the lung is different from that in the two preceding stereos. In this stereo the dorsal surface of the lung is directed obliquely towards the observer and the trachea is at the right; in the other two the dorsal surface of the lung is away from the observer and the trachea is at the top of the stereo.

SUMMARY

1. By the use of differential injection masses in the pulmonary arteries and veins the relations of these structures are plainly outlined by stereoroentgenograms.

2. Even though the pulmonary arteries be uninjected, they can be recognized in stereoroentgenograms as comparatively dense linear markings along the lateral wall of the bronchi. Under similar conditions the main venous trunk can be made out on the mesial side of the stem bronchus, but in its ultimate distribution its branches are not associated with the bronchi.

3. In reading X-ray plates care should be exercised not to mistake these linear markings for densities produced by pathological changes.

4. Ring-like shadows with sharp borders that appear along the bronchi are often due to the plane that the bronchi bear to the observer. When these ring-like shadows are broad, with irregular hazy borders, they are cast by bronchial cartilages.

5. This study suggests once more the importance of a knowledge of lung structure in interpreting densities cast on the X-ray plate.

REFERENCES

1. Aeby, C.: *Der Bronchialbaum der Säugethiere und des Menschen*, Engelmann, Leipzig, 1880, Taf. VI, Fig. 10.
2. Merkel, F.: *Handbuch der topographischen Anatomie*, Viegwig, Braunschweig, 1899, Bd. II, 399, Fig. 126.
3. Miller, W. S.: A differential injection mass for use with stereoroentgenograms, *Anat. Rec.*, 1918, XV, 47.

AN ELECTROMYOGRAPHIC STUDY OF CHOREA

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Graphic methods have been but little applied to the clinical study of neuromuscular phenomena; hence, our physiological conceptions of these conditions are vague. Chorea is one of the worst offenders. Most writers consider this disease from the endocarditic or infectious standpoint alone. Hertz,¹ in a paper on Babinski's second sign, and Wilson,² in his work on the lenticular nucleus and corpus striatum, have discussed some of the neurological problems, but even good clinical descriptions of the muscular movements are rare. Perhaps the best are by Osler,³ Weir Mitchell⁴ and Russell.⁵ The

paper by Gregor and Schilder⁶ is the only one that shows graphic records of choreiform movements.

The string-galvanometer has been used in the study of the skeletal muscles by Piper,⁷ who finds that when a muscle is voluntarily contracted a series of action-currents are recorded at the rate of about 50 per second as long as the contraction lasts. This rate takes into consideration only the main waves (*Hauptwellen*) and not the wavelets which are superimposed on the larger waves. Recently Forbes⁸ has criticized and amplified this work. By referring to either of

these authors a detailed description of the methods may be obtained. In brief the technique consists of placing over the muscle to be studied a non-polarizable electrode which leads off the action-currents of the contracting muscle to the string of the galvanometer, the circuit being completed through another similar electrode on the skin near the first but not over a contracting muscle. The movements of the galvanometer string are recorded on a moving film in the same way

as in making electrocardiograms. In fact an ordinary "heart station" apparatus can be easily adapted for making electromyograms.

In this way several cases of muscular contraction were studied: First, normal voluntary contractions; second, voluntary contractions affected by chorea; and lastly, involuntary choreic contractions. The results are tabulated in Table I.

TABLE I

Observation number	Name of patient	Diagnosis	Muscle from which record was taken	Character of contraction	Character of electromyogram	Rate of main waves per second	Total rate of main waves + wavelets per second	Approximate average potential of action-currents in millivolts
1	L. S. C.	Normal.	Gastrocnemius.	Voluntary.	Steady tetanus.	50	160	0.5
2	L. B. H.	Normal.	Flexor sublimis digitorum.	Voluntary.	Steady tetanus.	58	180	1.7
3	K. J.	Unaffected side in hemichorea.	Flexor sublimis digitorum.	Voluntary.	Steady tetanus.	62	120	1.3
4	K. J.	Unaffected side in hemichorea.	Flexor sublimis digitorum.	Voluntary.	Steady tetanus.	57	121	1.1
5	K. J.	Unaffected side in hemichorea.	Flexor sublimis digitorum.	Voluntary.	Steady tetanus.	60	107	0.9
6	K. J.	Unaffected side in hemichorea.	Flexor sublimis digitorum.	Voluntary.	Steady tetanus.	55	121	0.9
7	K. J.	Unaffected side in hemichorea.	Flexor sublimis digitorum.	Voluntary, unsteady.	Irregular tetanus.	69	115	1.5
8	N. K.	Chorea.	Flexor sublimis digitorum.	Voluntary, unsteady.	Irregular tetanus.	56	133	1.0
9	N. K.	Chorea.	Flexor sublimis digitorum.	Voluntary, unsteady.	Irregular tetanus.	55	102	0.8
10	N. K.	Chorea.	Flexor sublimis digitorum.	Voluntary, unsteady.	Irregular tetanus.	58	118	0.8
11	I. M. R.	Chorea.	Flexor sublimis digitorum.	Voluntary, unsteady.	Irregular tetanus.	50	104	0.5
12	I. M. R.	Chorea.	Flexor sublimis digitorum.	Voluntary, unsteady.	Irregular tetanus.	52	114	0.6
13	E. S.	Chorea.	Flexor sublimis digitorum.	Voluntary, unsteady.	Irregular tetanus.	56	110	0.7
14	E. S.	Chorea.	Flexor sublimis digitorum.	Voluntary, unsteady.	Irregular tetanus.	58	116	0.7
15	E. S.	Chorea.	Flexor sublimis digitorum.	Involuntary.	Short tetanus.	66	124	0.5
16	E. S.	Chorea.	Flexor sublimis digitorum.	Involuntary.	Short tetanus.	74	101	0.3
17	N. K.	Chorea.	Flexor sublimis digitorum.	Involuntary.	Short tetanus.	58	130	0.8
18	N. K.	Chorea.	Flexor sublimis digitorum.	Involuntary.	Short tetanus.	58	105	1.0
19	N. K.	Chorea.	Flexor sublimis digitorum.	Involuntary.	Short tetanus.	60	120	0.6
20	I. M. A.	Chorea.	Flexor sublimis digitorum.	Involuntary.	Short tetanus.	72	120	0.2
21	I. M. A.	Chorea.	Flexor carpi radialis.	Involuntary.	Short tetanus.	72	130	0.2
22	M. F.	Chorea.	Flexor sublimis digitorum.	Involuntary.	Short tetanus.	50	92	0.7
23	M. F.	Chorea.	Flexor sublimis digitorum.	Involuntary.	Short tetanus.	50	90	0.8

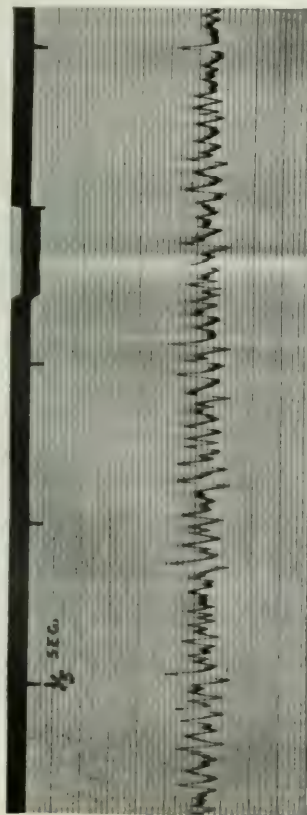


FIG. 1—Normal voluntary contraction of flexor sublimis digitorum.

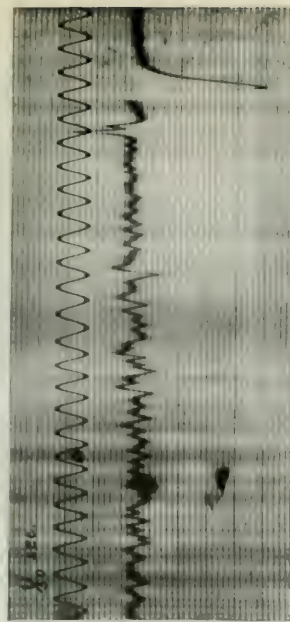


FIG. 4—Involuntary contraction in chorea. See table, observation No. 17.

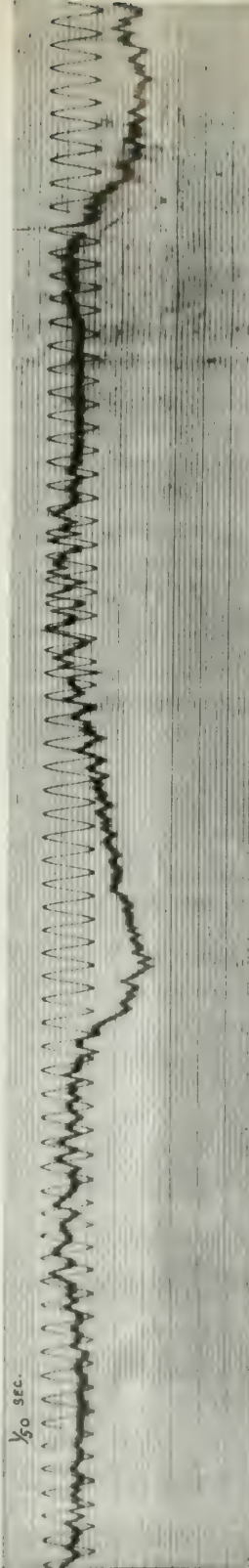


FIG. 2—Voluntary contraction in chorea, patient unable to maintain steady tetanus. See table, observation No. 10.

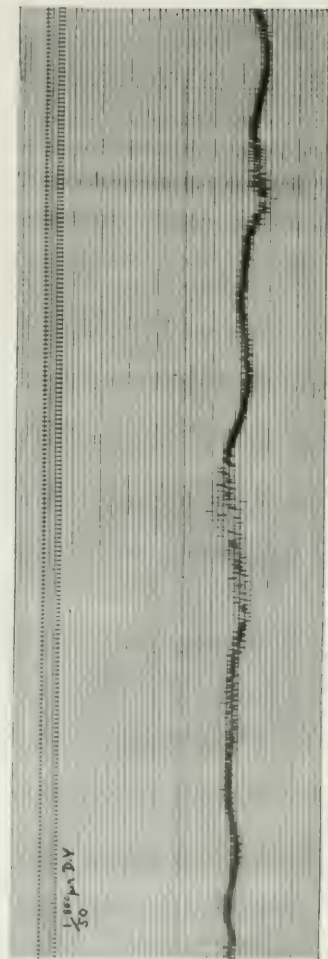


FIG. 3—Same as Fig. 2, but slow speed, showing an attempt to maintain steady contraction over a period of 41 seconds. See table, observation No. 11.



DISCUSSION

The tabulation of electromyographic records, as shown in Table I, shows that there is remarkably little qualitative difference between the action-current picture of a voluntary muscular contraction (Fig. 1)—whether it be in a normal or in a choreic individual—and that of an involuntary choreic movement (Fig. 4). Averaging the first six observations, those on *normally innervated muscles*, we get 57 main waves and a total of 135 if the wavelets are counted also. The average of the next eight observations, on *voluntary contractions of muscles affected by chorea*, gives the figures 57 and 113, respectively; while the records of *involuntary contraction*, nine in all, average 62 main waves and 123 total count per second. Quantitatively the normal voluntary contractions average 1.1 millivolts for an action-current, the voluntary contractions of affected muscles average 0.8 millivolt, and the involuntary contractions only 0.5 millivolt. This is what one would expect from the weakness clinically observed in these cases.

Gregor and Schilder give records from four cases of chorea, in which the rate of action-currents for voluntary contractions averages 54 per second, and for involuntary twitches 43 per second. This lower rate for the involuntary contractions is explained as possibly due to "a different localization for voluntary and for choreic movements, because in cortical innervation a rate of less than 50 per second is seldom found." It has been shown by Forbes and Rappleye¹¹ that the rate of action-currents in a muscle is dependent on the physiological state of that muscle; hence, "innervation" as used by Gregor, Schilder and Piper must be considered an erroneous term, for they seem to believe that each action-current represents a wave of nerve impulse. This subject has been further discussed by me in a paper on ankle clonus.¹² The fact that Gregor and Schilder found fewer action-currents per second in choreic twitches than in normal contractions may be due simply to the smaller amplitude of the waves registered on the film. The observations here published show that there is less electrical discharge in the weak contractions of a choreic movement than in the strong voluntary contractions (see Table I); hence, it may be gathered that the resistance of the patient might be enough to prevent any but the larger action-currents from registering. This should be taken into consideration and the apparatus readjusted when weak contractions are being recorded.

It seems therefore that the action-current pictures for voluntary and for choreic movement are essentially similar, except for their duration. Voluntary contractions are maintained over long periods, whereas choreic twitches may be as short as one-tenth of a second and show only four action-currents⁷ (Fig. 15); but usually they last from two-fifths to four-fifths of a second, occasionally longer. Wherein lies the difference, then, between normal and choreiform movements? Most authors speak of the abnormality as a lack of

co-ordination. Church and Peterson¹³ mention the "relaxation or sudden increase of muscular tension" during voluntary contraction; whereas, Dr. L. F. Barker well describes this in his clinics as a "failure of the ability to maintain tonic contraction." Just this point is illustrated by Figs. 2 and 3, where the patient was ordered and urged to grip the dynamometer steadily, but could not do so. The tracing shows variations in the size of action-currents, and in places complete failure of the action-currents. The slow undulations of the whole line are explained by the squirming of the wrist and arm coincident with the effort to grip, causing shifting of the leading-off electrodes on the skin.

In this connection it is interesting to turn to the work of Wilson³ (p. 483) on the corpus striatum, where he holds that this center is autonomous and exercises a "steadying influence" on the final common path of the pyramidal system via the lenticulo-rubro-spinal projection system. So it may be that in this form of chorea the "steadying influence" is lost, and with it the ability to maintain a steady contraction.

These electromyographic observations, therefore, seem to bring evidence which is of value in understanding the physiology of involuntary movements and the pathology of chorea. It is in the hope of stimulating others to study their neuromyopathic cases by this simple method, that this brief note is published.

CONCLUSIONS

1. Choreiform movements give an electromyogram similar to that of a short, normal, voluntary muscular contraction.
2. The inability to maintain voluntary contraction is clearly shown in the electromyograms.
3. Weakness of muscular contraction is shown electromyographically by the lessened electrical discharge.

BIBLIOGRAPHY

1. Hertz: *Rev. Neurol. and Psychiat.*, XII, 1914, 250.
2. Wilson: *Brain*, XXXIV, 1912, 295.
3. Wilson: *Brain* XXXVI, 1914, 428.
4. Osler: *On Chorea and Choreiform Affections*, Philadelphia, 1894, 29.
5. Mitchell and Rhein: *Philadelphia Med. Jour.*, January 22, 1898.
6. Russell: *Lancet*, April 1, 1899.
7. Gregor and Schilder: *Ztschr. f. d. g. Neurol. u. Psychiat.*, XIV, 1913, 359.
8. Piper: *Arch. f. Anat. u. Physiol. (Phys. Abth.)*, 1914, 345.
9. Piper: *Electrophysiologie Menschlicher Muskeln*, Berlin, 1912.
10. Forbes and Gregg: *Am. Jour. of Physiol.*, XXXVII, 1915, 118.
11. Forbes and Rappleye: *Am. Jour. of Physiol.*, XLII, 1917, 228.
12. Cobb: *J. H. H. Bull.*, XXIX, 1918.
13. Church and Peterson: *Nervous and Mental Diseases*, Philadelphia, 1903, 536.

A PHARMACOLOGICAL APPRECIATION OF A BIBLICAL REFERENCE TO MASS POISONING, II KINGS IV, 38-41*

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INTRODUCTORY

The Book of Books has played and still plays such an important rôle in the history of mankind and the history of civilization that any contribution conducing to a better understanding or appreciation of it should be welcomed. In the present paper I wish to discuss a Biblical passage which is of more than ordinary medical historical interest. No apology need therefore be made for presenting it before this distinguished Society for the study of the history of medicine.

The particular passage to which I am referring is in the Second Book of Kings, Chapter IV, verses 38 to 41 inclusive. It describes the accidental poisoning of a band of prophets and the means employed by their leader, the prophet Elisha, in combating it. This passage is of especial interest from the pharmacological and toxicological points of view. The narrative reads as follows:

And Elisha returned to Gilgal; and there was a famine in the land; and the sons of the prophets were sitting before him; and he said unto his servant, Set on the large pot, and seethe pottage for the sons of the prophets.

And one went out into the field to gather herbs, and found a wild vine, and gathered thereof *Paqqû'ôt*, his lapful, and came and shred them into the pottage; for they knew them not.

So they poured for the men to eat. And it came to pass as they were eating of the pottage, that they cried out, and said, O thou man of God, there is death in the pot! and they could not eat thereof.

But he said, Then bring meal. And he cast it into the pot; and he said: Pour out for the people that they may eat. And there was no harm in the pot.

The points of query suggested by the above passage and calling for elucidation are, firstly, what is meant by *Paqqû'ôt*; secondly, what are the pharmacological properties of the same; and thirdly, the most interesting of all, what can we say of the antidote here employed in the light of modern science? In order to shed light on these questions, it was necessary not only to gather, sift, and analyze a good deal historical, philological, archaeological, and botanical data, but also to perform a number of original pharmacological and toxicological experiments. The results of these inquiries and experiments we shall now proceed to describe.

ON THE MEANING OF PAQQÛ'ÔT

The Hebrew word *Paqqû'ôt* is rendered in the authorized version as "wild gourds" which, of course, may mean anything or nothing. All Biblical scholars and students of comparative philology, however, are agreed that the word *Paqqû'ôt* must mean either the *colocynthis* or *elaterium* fruit. The ety-

mology of the word, from a root *paqa'*, to burst or to break open, may apply appropriately to either one. *Ecballium elaterium* or the "squirting cucumber" owes its name to the peculiar character of its fruit which bursts open when ripe, ejecting the seeds mixed with a mucilaginous liquid. The colocynthis fruit, when ripe and dry, is also easily burst open on the slightest touch. Professor Haupt suggests that the root *paqa'*, to burst or break through or open, may also refer to the drastic effects of the drugs, both of which, as is well known, are violent purgatives and may produce vomiting. (Cf. the German word *brechen*, to vomit). The Septuagintal rendering *tolype* refers to the round fruit of *Citrullus colocynthis*. The Vulgate has *colocynthis* (Cf. Pliny, XX, 14).

While the term *Paqqû'ôt* may from the etymological point of view denote equally well the colocynthis or elaterium fruits, there is other evidence, botanical and archæological, which seems to point to the colocynthis as the correct translation. *Ecballium elaterium* (in Arabic, *kithâ el himâr*) is a common plant in Mediterranean countries, but it could not with any propriety, as pointed out by Post,¹ be called a vine, for it is destitute of tendrils. According to Baillon it is "une herbe couchée sans vrilles"—a decumbent herb, without tendrils.² The *Citrullus colocynthis*, on the other hand, is a true vine growing prostrate on the ground, but trailing by means of its powerful tendrils over shrubs and herbs. This plant is also common in the Jordan valley, but is rare in the hill country of Ephraim; so that the men who gathered it mistook it for another plant of the same family, the *Cucumis prophetarum*, or globe cucumber, common in Samaria.

Still further evidence suggesting that *Paqqû'ôt* or wild gourds denotes the colocynthis is the fact that we find the same term applied to the architectural ornaments mentioned in the Bible in connection with the Temple. In I Kings VI, 18, the word *p'qa'im* or colocynths is mentioned as an ornamental design in the interior woodwork of King Solomon's Temple; and in I Kings VII, 24, the same word is used to designate the ornaments encircling the molten sea or great brazen cistern in the Holy Temple. The elegant orange-shaped fruit of the colocynthis plant lends itself well for ornamental purposes, whereas the small olive-shaped fruit of the *Ecballium elaterium* is by no means so beautiful or attractive.^{3,4,5}

What do we know in regard to the poisonous properties of either the colocynthis or elaterium? Before proceeding to discuss the toxicology of these plants it may be well to describe briefly their physical and chemical characters.

PHARMACOGNOSY

Both the colocynthis and the elaterium plants belong to the family of the CUCURBITACEÆ or pumpkin family. The colocynthis fruit, *Fructus colocynthis*, or the English bitter apple.

* Read before the Historical Club of The Johns Hopkins Hospital, December 2, 1918.

and German *Colocynthis*, is the fruit of the plant *Citrullus colocynthis*, a slender scabrous plant with a perennial root, a native of warm and dry regions in the Old World. It is found in the Mediterranean regions, in Arabia, Syria and some of the Greek islands. (Fig. 1.) It grows in immense quantities in upper Egypt and Morocco, and is also found in some parts of Spain and Portugal. The plant bears yellow monœcious flowers, deeply lobed leaves and well-developed tendrils which enable it to trail over other plants. The fruit, which is globu-

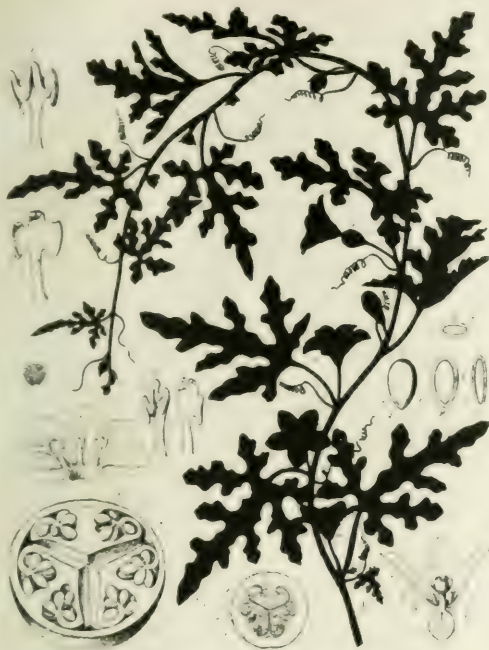


FIG. 1.—*Citrullus Colocynthis* Arn.

lar in shape, resembles an orange and has a smooth, marked green surface, being from 5 to 10 cm. or from 2 to 4 inches in diameter. For medicinal purposes, the colocynth fruit is dried in the sun, then peeled, and is sold in this form on the market. The pulp is white, very light and spongy and is readily separable longitudinally into three carpels, each containing numerous flat, ovate, white or light brown seeds. It is the pulp which is purgative in its nature. The seeds are not laxative at all and are said to be used in some parts of Africa for food. The active constituents of the colocynth fruits are at least two: one being the glucosid (?) *colocynthin*, having the empirical formula $C_{26}H_{44}O_{13}$, from which *colocynthin*, may be obtained by hydrolysis; the other is a closely related body named *colocynthitin*. Both of these principles are drastic purgatives."

The elaterium fruit comes from the *Echallium elaterium* Rich. (*Momordica elaterium* L.), a coarse, hispid fleshy

decumbent plant *without tendrils*, having a thick white perennial root. It is also common throughout the Mediterranean region, extending eastward as far as Southern Russia and Persia, and westward to Portugal. The fruit is ovoid and oblong and nodding, about 1.5 to 3 cm. long, with numerous short prickles terminating in white elongated points. It is attached by a long scabrous peduncle, is fleshy and green while young, becoming slightly yellowish when matured. It is three-celled and contains numerous oblong seeds lodged in a very bitter succulent pulp. The fruit when ripe separates suddenly from the stalk on the slightest jarring and at the same moment the seeds and juice are forcibly expelled from the aperture left by the detached peduncle—hence the name "squirting cucumber" (Fig. 2.)



FIG. 2.—*Echallium Elaterium*.

Several active principles have been isolated from the elaterium, the principal one, elaterin, being a crystalline body with a formula, $C_{26}H_{44}O_{13}$. Other constituents described are *hydroelaterin*, *prophetin* and *ecballin* or *elateric acid*. Both the colocynth and elaterium plants have been known from remote antiquity, and are mentioned by ancient writers, Pliny, Dioscorides, Theophrastus and others.

TOXICOLOGY

Colocynt and elaterium are well known in therapeutics as powerful or drastic purgatives. Even small doses of these drugs sometimes produce great irritation of the intestines. It will be remembered that colocynth is a constituent of the official compound cathartic pill, and elaterium has been named by one of the older therapeutists "the most potent purgative known to medicine." Slightly larger doses of the crude drugs, as well as of their active principles, produce a dangerous enteritis; and still larger doses act as violent poisons, leading to death.

The poisonous nature of these drugs was well known in the Orient. C. M. Doughty ("Travels in Arabia Deserta," Cambridge, 1888, vol. i, p. 132) says of the *Citrullus colocynthis*: "To human nature it is of so mortal bitterness that

little indeed, and even the leaf, is a most vehement purgative. They say it will leave a man half-dead, and he may only recover his strength by eating flesh meat."⁴

Kobert⁵ states that 4 gm. of colocynth pulp are fatal to human beings, and even smaller doses will produce vomiting, bloody stools, anuria, collapse, delirium and convulsions. Lewin⁶ gives 5 mg. of elaterin or 50 mg. of elaterium as the toxic dose for man and 60 mg. of elaterium as having produced death.

Von Jaksch⁷ regards doses of 30 to 50 mg. of elaterin as very poisonous. Craig⁸ reported death following the administration of two-fifths of a grain of the crude drug; and other writers emphasize even more strongly the dangers of this drastic purgative.

Poisoning with colocynth has, on the whole, been reported more frequently than with elaterin, possibly because the bitter apple has been employed to produce abortion.

Lewin mentions a case of fatal poisoning from 0.3 gm. of colocynth pulp. Blyth⁹ reports two similar cases. Christison¹⁰ reported the death of a young woman after one and a half teaspoonfuls of the powdered pulp. Rogers¹¹ mentions a fatal case after less than 60 grains of the powder; and other cases of poisoning are mentioned by Tidy,¹² Rolfe¹³ and others.

The symptoms of poisoning by both colocynth and elaterium described by various authors are those arising chiefly from irritation of the gastro-intestinal canal. Vomiting, bloody stools, severe colic, collapse and convulsions, followed by death, constitute the general course of the intoxication. In some cases, symptoms referable to intense irritation of the kidneys are encountered.

The pathological findings reported describe an intense congestion of the stomach and intestines with ecchymoses and bloody sero-fibrinous exudates with adhesions. In more protracted cases, more or less extensive peritonitis with matting of the intestines and congestion of the kidneys, liver and spleen, have been noted. The lumen of the intestines may actually be obliterated by the fibrinous exudate and adhesions of the intestinal walls.

TOXICOLOGICAL EXPERIMENTS

In order to study the symptoms of colocynth and elaterium poisoning more in detail, and in order to visualize better exactly what took place in the case of poisoning which we are discussing and especially in order to determine the value of the antidote employed in that case, the author has performed a number of toxicological experiments on dogs. In connection with these experiments, it was interesting to note a toxic symptom, which is not mentioned by most authors on the subject and not emphasized sufficiently by those who have noted it, and which is especially interesting in connection with the passage before us.

In my experiments I made use of infusions of either colocynth apples or the crude elaterium which can be bought on the market. The drugs were roughly cut up or ground up and infusions were made by boiling them in ordinary tap water in a casserole with or without the addition of a little common

table salt. This corresponded roughly to the conditions obtaining in the case of the prophets. After the mixture had been boiled for half an hour or longer, the resulting infusion was strained through coarse cheese-cloth and was administered cold to the dogs through a stomach-tube. The symptoms following the administration of such an infusion of colocynth apples may be divided into two groups, the primary and the secondary. The most striking primary symptom consisted of a profuse salivation which occurred even when the drugs were introduced through the stomach tube, enough of the infusion coming in contact with the mucous membranes of the mouth when the stomach tube was withdrawn to produce this irritation. The salivation was very intense; the animals foaming at the mouth more than after a dose of pilocarpin. This primary symptom, so little emphasized by other writers, is quite sufficient to account for the exclamation of the victims, "There is death in the pot!" Vomiting was occasionally also noted soon after administration of the infusions of colocynth. An almost precisely similar primary salivation followed the introduction of an elaterium infusion into the animal's stomach. Following the primary salivation and occasional vomiting, the secondary or later symptoms of colocynth or elaterium poisoning did not come on until an hour or two later. These began with violent purging, soon followed by bloody stools, collapse and depression. After large doses of either drug (the quantities to be described below) the animals were generally found dead on the following day. At autopsy, the anatomical findings were: Intense inflammation of the stomach and especially the intestines, with bloody exudate and adhesions; occasional peritonitis; intense congestion of the liver and the kidneys.

In view of the marked irritation and destructive lesions just described, it is especially interesting to turn our attention now to the most perplexing feature of our narrative, namely, the antidote administered or employed by the prophet Elisha to antagonize the effects of the poison.

ON FLOUR AS AN ANTIDOTE

In order to ascertain whether the method employed by Elisha can be explained on a natural basis the author in a purely scientific and impersonal manner carried out two series of experiments: In the one series, a number of dogs were given colocynth or elaterium infusions straight, that is, without the admixture of any other substance. In the other series exactly the same quantities of the infusions in proportion to the animal's weight, or even larger doses of the poisons were administered after previous admixture of ordinary corn and wheat flour. The results of these experiments are very interesting and enlightening and may be best illustrated by the following protocols:

Exp. V. October 7.—White dog weighing 7.1 kilos. Five colocynth apples, weighing together 40 gm., were cut up and boiled with 750 c.c. of tap water. The mixture was boiled until the volume was reduced to 500 c.c. It was then strained through coarse cheese-cloth and one-half of the infusion, or 250 c.c., were given to the animal through the stomach tube, about 2 p. m. Immediately after the removal of the stomach tube the dog

became most violently salivated, foaming and frothing at the mouth so that the whole cage was bespattered with saliva. A little of the infusion plus stomach contents was vomited out. Two hours later the animal was violently and repeatedly purged, the stools being fluid and tinged with blood. During the night, the frequent stools continued and assumed a much more bloody character. On the following morning, the animal was found dead. The autopsy revealed a violent congestion of the stomach, especially of the small intestine. The intestines were filled with a bloody exudate and in some places were stuck together by fibrinous adhesions. The liver also was congested and the kidneys to a very marked degree.

Exp. VI, October 7.—Brown dog weighing 6 kilos. Forty gm. of colocynth apples were cut up and mixed with 60 gm. of flour (equal parts of wheat and corn) and 1000 c. c. of tap water. The mixture was boiled until the total volume was reduced to 500 c. c. It was then strained, in order to remove the seeds and débris, through coarse cheese-cloth, and 250 c. c. of the broth were administered to the dog through a stomach tube exactly as in the preceding experiment, about 2.15 p. m. On removal of the stomach tube there was no vomiting and practically no salivation noted. About two hours later, the animal passed several normal stools, but no blood was noted in them; neither was there any blood noted in the stools passed during the night. On October 8, the animal was lying slightly depressed and still had diarrhoea, but ate the food offered it. On October 9, the animal was apparently completely recovered, running about in a lively fashion.

On comparing the two experiments described above, it will be seen that in the case of the dog to which the pure infusion of colocynth was administered, both the primary and the later symptoms of colocynth poisoning were very markedly developed, and in this respect differed from those noted in the other animal. The white dog was very profoundly salivated; indeed, the salivation was more marked than that noted by the author after any other poison. Violent irritation of the bowels very early manifested itself as indicated by the bloody stools; and the animal died within 18 hours.

In the dog to which the infusion of colocynth was administered together with flour the symptoms were not at all so striking. There was practically no salivation at all and no vomiting; nor did the stools indicate any violent irritation of the intestinal mucosa; and the animal recovered completely within two days.

Exactly similar results were noted in experiments with elaterium, as may be illustrated by the following two protocols:

Exp. VII, October 22.—White dog weighing 4 kilos. Five gm. of dried elaterium juice or exudate, obtained from the firm of Sharp & Dohme through the courtesy of Dr. H. D. Engelhardt, were pulverized in a mortar and then boiled for half an hour in 300 c. c. of tap water with the addition of a little common table salt. Of this mixture 150 c. c. were then introduced into the stomach through a stomach tube at about 11.30 a. m. Immediately after withdrawal of the tube, the animal became very much salivated. About 2 p. m. a black, bloody stool was passed. Repeated purgation occurred during the night and on the following morning the animal was found dead. An autopsy revealed anatomical lesions very much as in the case of colocynth poisoning, though perhaps more intense in degree.

Exp. VIII, October 22.—Brown dog weighing 5 kilos. Six gm. of dried elaterium juice or exudate were ground in a mortar and mixed with 15 gm. of flour and the mixture was boiled for half an hour with 300 c. c. of water. At 11.40 a. m. about 175 c. c. of the

broth were introduced through the stomach tube into the animal's stomach. On withdrawal of the stomach tube there was no vomiting and practically no salivation. About two hours later, a yellow stool was passed and several other fluid but not bloody stools were passed during the night. On the following morning, October 23, the animal was found very much depressed, lying quietly in the cage and refusing food. On October 24, the animal was still depressed, but ate meat. On October 25, the animal was more lively and hopping about. October 27, the dog was practically in normal health.

In the case of the elaterium it will be noted again that the plain infusion was much more toxic when given alone than when administered mixed with flour broth. In the first case, salivation, bloody stools and death followed, whereas in the second case, although there were diarrhoea and depression, no salivation was noted, no violent irritation occurred and the animal eventually recovered.

DISCUSSION

To the superficial reader of the Bible and to a class of destructive critics who are prone to condemn any statement in that Book, which does not accord with their own personal subjective views, as an impossibility or a figment of the imagination or as a perversion of the original text, the results of the above investigations may appear unexpected and possibly even disappointing. To the truly unbiased scientific mind, however, which does not condemn or disbelieve anything, but only demands facts and proofs, the above experiments are not altogether surprising and the Biblical narrative which we are discussing does not appear at all improbable. In fact, the results of the experiments just described well agree with the teachings of modern chemistry and pharmacology. Recent advances in those sciences have revealed the very important rôle played in the physiological economy of animal organisms by the so-called "colloid" substances. It has been shown that an admixture of colloidal and even of non-colloidal but inert and inactive matter to various foods and drugs may profoundly influence their absorption and their action. Thus, for instance, Mendel and Lewis² in a paper on "The Rate of Elimination of Nitrogen as Influenced by Diet and Other Factors," have found that with a definite diet it is always possible to get a definite typical curve of nitrogen elimination. On the addition, however, of various inert or colloidal substances, such as minerals, vaseline, bone ash, filter paper, cork, agar-agar, etc., to exactly the same diet, the curve is entirely changed, and the rate of nitrogen elimination in such cases is greatly delayed.

Again, Fantus³ and others have found that admixture of kaolin and other inert matter may greatly modify the action of strychnin and other poisons. It is, therefore, not entirely surprising to find that flour or "meal" should profoundly modify the action of the infusions of colocynth or elaterium and render them innocuous, and the popular first aid maxim to give flour in many cases of poisoning has a real rational basis. What the exact mechanism of this antagonistic action is, is not quite clear; but undoubtedly several factors are involved in the phenomenon. The colloid broth, in the first place,

hinders the absorption of the poison; secondly, the flour probably acts as a demulcent and protective to the intestinal walls; and thirdly, this substance must also exert some effect by virtue of its adsorptive properties. Whatever the exact mechanism of flour as an antidote may be, there can hardly be any doubt as to the plausibility of the Biblical narrative before us; and in the light of the experiments performed, the story, if not a miraculous one, certainly attests to the wonderful insight and wisdom and practical experience of the Seer Elisha.²⁸

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LITERATURE

1. Post: in Hastings' Dictionary of the Bible, II, p. 250a.
2. Baillon: Dictionnaire de Botanique, 1886, t. 2, p. 493.
3. Jewish Encyclopedia, III, p. 357.
4. Hamburger: Real-Encyclopädie des Judentums, Th. I, p. 500.
5. Nowack: Lehrbuch der Hebräischen Archaeologie, 1894, Bd. II, p. 42.

6. Benzinger: Archaeologie, 1894, p. 252.
7. Pickering: History of Plants, 1879, p. 249.
8. Husemann und Hilger: Pflanzenstoffe, Berlin, 1884, p. 1347.
9. Idem, Pflanzenstoffe, Berlin, 1884, p. 1350.
10. Flückiger und Hanbury: Pharmacographia, 1879.
11. Kramers: Pharmacognosy, 1917.
12. United States Dispensary, 1917.
13. National Dispensary, 1917.
14. Hastings: Dictionary of the Bible, II, p. 28b.
15. Kobert: Intoxikationen, 1906, II, Th. 2, p. 560 ff.
16. Lewin: Toxikologie, 1897, p. 298.
17. Jaksch (von): Vergiftungen, 1910, p. 549.
18. Craig: J. M. Indianap., 1868, III, p. 283.
19. Blyth: Poisons, 1895, p. 30.
20. Christison: Cited by Taylor in his Manual of Med. Jurisprudence, 1897, p. 168.
21. Rogers: Cited by Taylor in his Manual of Med. Jurisprudence, 1897, p. 168.
22. Tidy: Lancet (London), 1868, I, p. 118.
23. Rolfe: Boston M. & S. Jour., 1892, CXXVI, p. 494.
24. Mendel and Lewis: Jour. Biol. Chem., 1913, XVI, p. 19.
25. Fantus: Jour. A. M. A., 1913, LXVII, p. 1838.
26. Bayliss: General Physiology, 1915 (Chaps. on Surface Action and Colloid Solutions).

TITLES OF PAPERS APPEARING DURING THE YEAR, ELSEWHERE THAN IN THE BULLETIN, BY PRESENT AND FORMER MEMBERS OF THE HOSPITAL AND MEDICAL SCHOOL STAFF

ABEL, J. J., and PINCOFFS, M. C.

On the presence of albumins in extracts of the posterior lobe of the hypophysis cerebri.—*Stud. Rockefeller Inst. M. Research*, N. Y., 1918, xxviii, 193-203.

ATCHLEY, D. W.

A study of eight cases of acute nephritis.—*Arch. Int. Med.*, Chicago, 1918, xxii, 370-408.
Renal action in acute nephritis.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1917-18, xv, 85-88.

AUER, J.

Generalized analgesia in cats after exposure to a war gas (CH_3SO_4).—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1918, xv, 104-106.
Localized pulmonary edema in cats after the inhalation of war gas (CH_3SO_4).—*Ibid.*, 106-107.

AUER, J., and GATES, F. L.

Experiments on the causation and amelioration of adrenalin in pulmonary edema.—*Stud. Rockefeller Inst. M. Research*, N. Y., 1918, xxviii, 131-150.

AUER, J., and KLEINER, ISABEL S.

Morphine hyperglycemia in dogs with experimental pancreatic deficiency.—*J. Exper. Med.*, Balt., 1918, xxvii, 49-63.

AUER, J., and MELTZER, S. J.

Lantern slide demonstration of the effect of magnesium sulphate upon tetanus.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1917-18, xv, 36-37.
The administration of epinephrin by intraspinal injections in acute or subchronic cases accompanied by a low blood pressure.—*J. Am. M. Ass.*, Chicago, 1918, lx, 70-71.

BAER, W. S.

Arthroplasty with the aid of animal membrane.—*Am. J. Orthop. Surg.*, Bost., 1918, xvi, 1-29; 94-115; 171-199.
Primary and delayed primary suture in the treatment of war fractures.—*Am. J. Orthop. Surg.*, Bost., 1918, xvi, 513-519.
Also: *J. Am. M. Ass.*, Chicago, 1918, lx, 1530-1533.

BAETJER, F. H.

Differential diagnosis of bone tumors.—*Am. J. Roentgenol.*, N. Y., 1918, v, 261-264.

BAETJER, W. A., and MILLER, S. R.

Bence-Jones proteinuria: some observations on its occurrence, with particular reference to nephritis and hypertension.—*J. Am. M. Ass.*, Chicago, 1918, lx, 137-139.
Pollinosis or hay-fever: its specific treatment.—*South. M. J.*, Birmingham, Ala., 1918, xi, 341-345.

BAETJER, W., STRONG, R. P. [et al.].

Report on progress of trench fever investigations. Trench Fever Commission of Medical Research Committee, American Red Cross.—*J. Am. M. Ass.*, Chicago, 1918, lx, 1597-1598.

BARKER, L. F.

Heart murmurs.—*Canada Lancet*, Toronto, 1918, ii, 545-551.
Endocrine functions and the digestive apparatus. *Med. & Surg.*, St. Louis, 1918, ii, 655-678.
The general diagnostic study by the internist.—*N. York M. J.* [etc.], 1918, cvii, 489-493; 538-542; 577-582. Also: *Med. Rec.*, N. Y., 1918, Nervous and mental symptoms in ophthalmic goiter.—*J. Am. M. Ass.*, Chicago, 1918, lx, 327-329.
The value of the classics as a part of the studies preparatory to medicine.—*South. M. J.*, Birmingham, Ala., 1918, xi, 391-394.
Address in Medicine. On the significance of "heart murmurs" that may be found on examination of candidates for military service.—*Canad. M. Ass. J.*, Toronto, 1918, viii, 577-585.
Oral sepsis and the digestive apparatus.—*South. M. J.*, Birmingham, Ala., 1918, xi, 481-484.
The first ten years of the National Committee for Mental Hygiene, with some comments on its future.—*Ment. Hyg.*, Concord, N. H., 1918, ii, 557-581.

BARKER, L. F., and MILLER, S. R.

Perforating ulcer of the hard palate resembling tertiary syphilis.—*J. Am. M. Ass.*, Chicago, 1918, lxix, 793-797.

BARKER, L. F., and ROWNTREE, L. G.

A report of a case of myrtle poisoning with comments upon the toxicity of eucalyptus oil and myrtle in human beings and in animals.—*Tr. Ass. Am. Physicians*, Phila., 1918, xxxiii.

BEALL, K. H.

The diagnosis of nephritis.—*Texas State J. M.*, Fort Worth, 1918, xlii, 349-351.

BERRY, J. M.

Action of the gluteus maximus and pyramidalis muscles in sacro-liliac strain.—*Albany M. Ann.*, 1918, xxxix, 258-263.

BLACKFAN, K. D.

Lead poisoning in children.—*Midland M. J.*, Birmingham, 1918, xvii, 5-7.

BLACKFAN, K. D., and MAXCY, K. F.

The intraperitoneal injection of saline solution.—*Am. J. Dis. Child.*, Chicago, 1918, xv, 19-28.

BLOCK, E. B.

The relation of oral sepsis to the nervous system.—*South. M. J.*, Birmingham, Ala., 1918, xi, 606-609.

BLOODGOOD, J. C.

Some hernias that disqualify for military service, whether operated on or not.—*J. Am. M. Ass.*, Chicago, 1918, lxix, 515.
A warning against operations for varicose on applicants for enlistment, registrants for the selective draft and soldiers.—*J. Am. M. Ass.*, Chicago, 1918, lxix, 409.
Medical preparedness and medical and surgical problems in this war.—*Fenn. M. J.*, Athens, Pa., 1918, xxi, 389-394.
Medical preparedness in the great drive for democracy.—*South. M. J.*, Birmingham, Alabama, 1918, xi, 51-56.

- Also: *Maryland M. J.*, Balt., 1918, lxi, 1-9.
Also: *J. Florida M. Ass.*, St. Augustine & Jacksonville, 1918, iv, 255-260.
How the industrial surgeon can best co-operate with the Government during the war. *South M. J.*, Birmingham, Ala., 1918, xl, 453-454.
The importance of recognizing the weakness or the obliteration of the conjoint tendon in operations for inguinal hernia.—*South M. J.*, Birmingham, Alabama, 1918, xl, 366-369.
Also: *West. M. Rev.*, Omaha, Neb., 1918, xxiii, 394-397.
Soldiers disabled in the war. (Letter).—*South M. J.*, Birmingham, Alabama, 1918, xl, 62-65.
Some principles involving the treatment of infected wounds. *J. Med. Ass. Georgia*, Augusta, 1918, viii, 9-13.
- BLOOMFIELD, A.**
Typhoid bacteremia during the course of millary tuberculosis.—*Am. Rev. Tuberc.*, Balt., 1918, ii, 28-35.
- BREM, W. V., BOLLING, G. E. and CASPER, E. J.**
Pandemic influenza and secondary pneumonia at Camp Fremont, Calif.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 2138-2144.
- BRIDGMAN, E. W., and HIROSE, K.**
The effect of diuretics on the general blood pressure in animals with constriction of the renal arteries.—*Arch. Int. Med.*, Chicago, 1918, xxi, 351-353.
- BROOKS, B., and ALLISON, N.**
Arthroplasty: experimental and clinical methods.—*Am. J. Orthop. Surg.*, Boston, 1918, xvi, 83-93.
- BROOKS, B., SCHUMACHER, H. W., and WATTENBERG, J. E.**
Intestinal obstruction: an experimental study.—*Ann. Surg.*, Phila., 1918, lxxvii, 210-214.
- BROWN, T. R.**
Studies on some unusual types of diarrhea.—*Med. & Surg.*, St. Louis, 1918, ii, 840-845.
- BUNTING, C. H., MARTIN, H. G., and LOEVENHART, A. S.**
The morphological changes in the tissues of the rabbit as a result of reduced oxidation.—*J. Exper. M.*, Balt., 1918, xxvii, 399-412.
- BURNS, J. E.**
The diagnosis and treatment of urinary lithiasis.—*West Virg. M. J.*, Huntington, 1918, xii, 286-291.
- BURNS, J. E., and HOPKINS, P. B.**
A comparative study of the effects of thorium and other substances on the renal parenchyma when retained.—*J. Urol.*, Balt., 1918, ii, 145-159.
- BURROWS, M. T.**
A note on the mechanism of heart muscle contractions.—*J. Missouri M. Ass.*, St. Louis, 1918, xv, 138.
Why should autopsies be held? The argument to be used with relatives and friends.—*Interstate M. J.*, Chicago, 1918, xxv, 760-763.
- BURROWS, M. T., and NEYMANN, C. A.**
Studies on the metabolism of cells in vitro. The toxicity of dipeptides for embryonic chicken cells.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1918, xv, 138-140.
- CAMAC, C. N. B.**
Clinical report upon cases of lobar pneumonia treated with anti-pneumococcus serum as observed at general hospital no. 6, Fort McPherson, Georgia, October, 1917, to May, 1918.—*Am. J. M. Sc.*, Phila., 1918, civl, 887-893.
- CAMERON, D. F.**
Aqueous solutions of potassium and sodium iodides as opaque mediums in roentgenography. Preliminary report.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 754-755.
- CAMERON, D. F., and GRANDY, C. C.**
Sodium and potassium iodides in roentgenography.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1516-1517.
- CAMPBELL, C. M.**
The rôle of instinct, emotion and personality in disorders of the heart. With suggestions for a clinical record.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 1621-1626.
A city school district and its subnormal children: with a discussion of some social problems involved and suggestions for constructive work.—*Ment. Hyg.*, Concord, N. H., 1918, ii, 232-244.
A case of childhood conflicts with prominent reference to the urinary system; with some general considerations on urinary symptoms in the psychoneuroses and psychoses.—*Psychosomati. Rev.*, Wash., 1918, v, 269-296.
- CARTER, E. P.**
Further observations on the aberrant electrocardiogram associated with sclerosis of the atrioventricular bundle branches and their terminal arborizations. Clinical and histologic report of a case in which such aberrant complexes were obtained.—*Arch. Int. Med.*, Chicago, 1918, xxvii, 561-565.
- CARTER, E. P. and WEDD, A. M.**
Report of a case of paroxysmal tachycardia characterized by unusual control of the fast rhythm.—*Arch. Int. Med.*, Chicago, 1918, xxii, 571-580.
- CASIER, DEW. B.**
Tetanus following laparotomy for ectopic pregnancy. Treatment by subarachnoid injections of magnesium sulphate and antitetanic serum—recovery.—*South M. J.*, Birmingham, Ala., 1918, xl, 512-516.
- CAULK, J. R.**
Infections of the bladder.—*In: Mod. Urol.*, (Cabot), 8th, Phila. & N. Y., 1918, ii, 80-131.
The treatment of undescended testicle.—*Interstate M. J.*, St. Louis, 1918, xxv, 285-286.
The diagnosis of diseases of the central nervous system by means of the cystoscopic appearance of the bladder.—*Interstate M. J.*, St. Louis, 1918, xxv, 102-104.
Remarks on kidney surgery.—*South M. J.*, Birmingham, Ala., 1918, xl, 299-305.
- CAULE, J. R., and GREUTZGER, H. C.**
Occluded renal tuberculosis, autonephrectomy.—*Med. & Surg.*, St. Louis, 1918, ii, 453-456.
- CECIL, A. B.**
An unique type of urethral obstruction.—*J. Urol.*, Balt., 1918, ii, 379-384.
- CHESNEY, A. M., and CULLEN, G. E.**
A note on the production of acid by pneumococci.—*J. Exper. M.*, Balt., 1918, xxvii, 289-290.
- CHESNEY, A. M., and MOORE, H. F.**
A further study of ethylhydrocuprein (optochin) in the treatment of acute lobar pneumonia.—*Arch. Int. Med.*, Chicago, 1918, xxi, 659-681.
- CHURCHMAN, J. W.**
Melanosarcoma of the rectum, with the report of a case.—*Am. J. M. Sc.*, Phila., 1918, civ, 639-644.
Treatment of acute infections of the joint by lavage and direct medication.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1047-1050.
Fibroma of the tongue with consideration of other tumors of the tongue and certain technical points in tongue resections.—*Med. & Surg.*, St. Louis, 1918, ii, 173-177.
A new incision for exposure of the lower abdomen and pelvis.—*Ann. Surg.*, Phila., 1918, lxxvii, 180-182.
- CLARK, A. H., and FELTON, L. D.**
A filtrable toxic product of the hemolytic streptococcus.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 1048-1049.
- CLARK, J. G.**
Medical teaching and research after the war.—*Am. J. Obst.*, N. Y., 1918, lxxviii, 220-230.
The therapeutic use of radium in gynecology.—*Surg. Gynec. & Obst.*, Chicago, 1918, xxvi, 610-624.
- CLARKE, T. W.**
The baby that cannot take milk.—*Arch. Pediat.*, N. Y., 1918, xxxv, 193-225.
- CLAUSEN, S. W.**
A method for the estimation of potassium in blood.—*J. Biol. Chem.*, Balt., 1918, xxxvi, 479-484.
The effect of injections of pituitary solution on the urinary output in a case of diabetes insipidus.—*Am. J. Dis. Child.*, Chicago, 1918, xvi, 195-204.
- CLAUSEN, S. W., and MOSENTHAL, H. O.**
The maintenance diet in diabetes mellitus as determined by the nitrogen equilibrium.—*Arch. Int. Med.*, Chicago, 1918, xxi, 200-281.
- CLAUSEN, S. W., MOSENTHAL, H. O., and HILLER, ALMA.**
The effect of diet on blood sugar in diabetes mellitus.—*Arch. Int. Med.*, Chicago, 1918, xxi, 93-108.
- COBB, S.**
A note on the supposed relation of the sympathetic nerves to decrease brate rigidity, muscle tone, and tendon reflexes.—*Am. J. Physiol.*, Balt., 1918, xlvi, 478-482.
- COLE, R.**
Prevention of pneumonia.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 635-639.
Pneumonia as a public health problem.—*Kentucky M. J.*, 1918, xvi, 563-565.
- COLE, R., and MACCALLUM, W. G.**
Pneumonia at a base hospital.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1146-1156.
- COSE, S. M.**
A method of studying nerves.—*Am. J. Orthop. Surg.*, Bost., 1918, xvi, 42-43.
Some of the results of work on the pathology of post-phalangeal nerve injuries.—*Am. J. Orthop. Surg.*, Bost., 1918, xvi, 119-122.
Surgical pathology of the peripheral nerves.—*Brit. J. Surg.*, Bristol, 1917-18, v, 724-777.
Histological observations on normal nerves and over-injured nerves with the neurokeratin stain.—*J. Path. & Bacteriol.*, Lond., 1918, xvi, 105-111.
- CORNER, G. W., and HURST, F. H.**
The non-effect of corpus luteum preparations on the ovulation cycle of the rat.—*Am. J. Physiol.*, Balt., 1918, xlvi, 483-486.
- CUSHING, H.**
A study of a series of wounds involving the brain and the developing structure.—*Brit. J. Surg.*, Bristol, 1917-18, v, 558-604.
Notes on penetrating wounds of the brain.—*Brit. M. J.*, Lond., 1918, i, 221-226.
- DANDY, W. E.**
Excystation of the choroid plexus of the lateral ventricles in communicating hydrocephalus.—*Ann. Surg.*, Phila., 1918, lxxvii, 569-579.
Ventriculography following the injection of air into the cerebral ventricles.—*Ann. Surg.*, Phila., 1918, lxxvii, 5-11.

- DAVIS, E. G.
Duodenal ureteral fistula of spontaneous origin: report of a case.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 376-378.
Urinary antiseptics: a study of the antiseptic properties and the renal excretion of compounds related to phenolsulphonophthalein: preliminary report.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 581-585.
- DAVIS, E. G., and HAIN, R. F.
Urinary antiseptics. The antiseptic properties of normal dog urine.—*J. Urol. Balt.*, 1918, ii, 309-320.
- DAVIS, E. G., and HARRELL, B. E.
Acridiflavine in the treatment of gonorrhea—an experimental and clinical study.—*J. Urol. Balt.*, 1918, ii, 257-276.
- DAVIS, E. G., and WHITE, E. C.
Urinary antiseptics, further studies of the antiseptic properties and the renal excretion of compounds related to phenolsulphonophthalein.—*J. Urol. Balt.*, 1918, ii, 107-127.
Urinary antiseptics. The secretion of antiseptic urine following the intravenous administration of acridiflavine and proflavine: preliminary report.—*J. Urol. Balt.*, 1918, ii, 299-307.
- DAVIS, E. G., WHITE, E. C., and ROSEN, R.
Urinary antiseptics. The secretion of antiseptic urine following the intravenous administration of an organo-mercury phthalein derivative.—*J. Urol. Balt.*, 1918, ii, 277-297.
- DAVIS, E. G., and YOUNG, H. H.
The surgery of the double kidney. Report of a case of resection of upper segment for calculous pyonephrosis.—*Surg., Gynec. & Obst.*, Chicago, 1918, xxvii, 1-13.
- DAVIS, J. S.
The use of the pedunculated flap in reconstructive surgery.—*Ann. Surg.*, Phila., 1918, lxxviii, 221-230.
- DAVISON, W. C.
The superiority of inoculations with mixed triple vaccine (B. typhosus, B. paratyphosus A. and B. paratyphosus B.) over successive inoculations with the single vaccines as shown by agglutinin curves in men and rabbits.—*Arch. Int. Med.*, Chicago, 1918, xli, 437-509.
- DAWSON, P. M.
University ideals and their limitations.—*Science*, N. Y. and Lancaster, Pa., 1918, n. s., xlvii, 547-550.
- DICK, GLADYS H., and MURRAY, ELEANOR.
The morphology of the influenza bacillus.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 1568.
- DICKSON, E. C.
Botulism: a further report of cases occurring in the Pacific Coast States.—*Arch. Int. Med.*, Chicago, 1918, xxvii, 483-495.
Botulism. A clinical and experimental study.—*Monogr. Rockefeller Inst. M. Research*, N. Y., 1918, no. 8.
Botulism.—*Bull. Canadian Army M. Corps*, 1918, i, 85-87.
Also: *Canad. M. Ass. J.*, 1918, viii, 903-909.
- DICKSON, E. C., and BURKE, G. E.
Botulism: a method of isolating *Bacillus Botulinus* from infected materials.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 518-521.
- FELTON, L. D., and CLARK, A. H.
A filtrable toxic product of the hemolytic streptococcus.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 1048-1049.
- FLEXNER, S.
Control of meningitis.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 638-639.
Dr. Franklin P. Mall: an appreciation.—*Science*, N. Y. & Lancaster, Pa., 1918, n. s., xlvii, 240-254.
- FLEXNER, S., and AMOSS, H. L.
The passage of neutralizing substance from the blood into the cerebrospinal fluid in actively immunized monkeys.—*J. Exper. M. Balt.*, 1918, xxviii, 11-17.
- FLEXNER, S., AMOSS, H. L., and EBERSON, F.
Physiological stimulation of the choroid plexus and experimental poliomyelitis.—*J. Exper. M. Balt.*, 1918, xxvii, 679-687.
- FLOURNOY, H.
Notes sur 4 cas d'obsessions et impulsions à début instantané.—(Communication à la Société Médicale de Genève, Genève, 1918, Kündig, 24 pp. 8.
L'alcoolisme et les enfants anormaux.—Extrait du xlii rapport de la Société genevoise de patronage des Aliénés, 1918, 16 pp. 8.
- FORD, W. W.
Further observations on the bacteria of the intestinal tract.—*Tr. Ass. Am. Physicians*, Phila., 1918, xxxiii.
- FOWLER, H. A.
Anatomy, anomalies and injuries of the penis.—*In: Mod. Urol.* (Cabot), 8^o, Phila. & N. Y., 1918, i, 193-222.
- FRONTZ, W. A.
Presentation of device facilitating the introduction of the cystoscope in certain difficult cases.—*J. Urol. Balt.*, 1918, ii, 39-41.
- FRONTZ, W. A., and GERAGHTY, J. T.
A study of primary hydronephrosis.—*J. Urol. Balt.*, 1918, ii, 161-209.
- FUTCHER, T. B.
Chronic hypertrophic pulmonary osteo-arthritis following bronchiectasis.—*Bull. Canad. Army Med. Corps*, 1918, i, 38-40.
- GABRIER, J. R.
A plea for prenatal care and the end-results of the hygiene of pregnancy.—*Am. J. Obst.*, N. Y., 1918, lxxviii, 566-575.
- GATCH, W. D.
Some observations on the surgery of the thyroid gland.—*J. Indiana M. Ass.*, Fort Wayne, 1918, xi, 13-17.
- GERAGHTY, J. T.
Tumors of the bladder.—*In: Mod. Urol.* (Cabot), 8^o, Phila. & N. Y., 1918, ii, 187-244.
Tests of renal function.—*In: Mod. Urol.* (Cabot), 8^o, Phila. & N. Y., 1918, ii, 337-376.
The results of treatment of bladder tumors.—*Radium*, Pittsburgh, Pa., 1918, x, 77-85.
- GERAGHTY, J. T., and FRONTZ, W. A.
A study of primary hydronephrosis.—*J. Urol. Balt.*, 1918, ii, 161-209.
- GIBBS, J. H.
Hodgkin's disease: primary involvement of mediastinal glands with presentation of tumor mass over sternum. Blood-picture characteristic of well-advanced disease. Differential diagnosis. Etiology. Pathologic anatomy. Prognosis. Treatment.—*Med. Clin. N. Am.*, Phila., 1917-18, l, 1587-1594.
Oral sepsis and arthritis.—*South. M. J.*, Birmingham, Ala., 1918, xi, 489-492.
- GIFFIN, H. Z.
Splenectomy following radium treatment for myelocytic leukemia.—*Med. Rec.*, N. Y., 1918, xciv, 1020-1023.
- GIFFIN, H. Z., SANFORD, A. H., and SZLAPKA, T. L.
Estimation of urobilin and urobilinogen in the duodenal contents.—*Am. J. M. Sc.*, Phila., 1918, civ, 562-579.
- GOETSCH, E.
Newer methods in the diagnosis of thyroid disorders: pathological and clinical.—*N. York State J. M.*, N. Y., 1918, xxvii, 259-267. Also: *Clifton Med. Bull.*, Clifton Springs, 1918, 1-12.
- GOLDBACH, L. J.
Naso-pharyngeal fibro-myxoma, undergoing sarcomatous changes.—*Laryngoscope*, St. Louis, 1918, xxviii, 106-108.
- GOODPASTURE, E. W.
An anatomical study of senescence in dogs, with especial reference to the relation of cellular changes of age to tumors.—*J. Med. Research*, Bost., 1918, xxxviii, 127-190.
Observations on mitochondria of tumors.—*Ibid.*, 213-224.
- GOODPASTURE, E. W., and JACOBSON, V. C.
Occlusion of the entire inferior vena cava by hypernephroma, with thrombosis of the hepatic vein and its branches.—*Arch. Int. M.*, Chicago, 1918, xxii, 86-93.
- GORHAM, L. W.
Note on the diagnostic use of the X-ray in pneumonia, with especial reference to the position of the diaphragm.—*Albany M. Ann.*, 1918, xxxix, 58-65.
- GREY, E. G.
Observations on the postural activity of the stomach.—*Am. J. Physiol.*, Balt., 1918, xlv, 272-285.
- GRIFFITH, F. W.
Some of the common errors in gynecology.—*South. M. J.*, Birmingham, Ala., 1918, xi, 40-42.
- GUNDRUM, F. F.
Rat bite fever with report of two cases.—*Calif. State J. M.*, San Fran., 1918, xvi, 16-18.
Nitro-benzol poisoning.—*Calif. State J. M.*, San Fran., 1918, xvi, 252-253.
- HAIN, R. F., and DAVIS, E. G.
Urinary antiseptics. The antiseptic properties of normal dog urine.—*J. Urol. Balt.*, 1918, ii, 309-320.
- HALSTED, W. S.
Dilation of the great arteries distal to partially occluding bands.—*Proc. Nat. Acad. Sc.*, Balt., 1918, iv, 204-210.
Cylindrical dilation of the common carotid artery following partial occlusion of the innominate and ligation of the subclavian.—*Tr. Am. Surg. Ass.*, Phila., 1918, xxxvi.
Letter to Dr. Keen. Communication on the subject of the Carrel-Dakin treatment of wounds. *In: Keen, W. W.* The treatment of war wounds, Phila., 2. ed., 1918, 252-259.
- HARRELL, B. E., and DAVIS, E. G.
Acridiflavine in the treatment of gonorrhea—an experimental and clinical study.—*J. Urol. Balt.*, 1918, ii, 257-276.
- HARROP, G. A., and MOSENTHAL, H. O.
The comparative food value of protein, fat and alcohol in diabetes mellitus as measured by the nitrogen equilibrium.—*Arch. Int. Med.*, Chicago, 1918, xli, 750-758.
- HAZEN, H. H.
Syphilis and the war.—*Am. J. Syph.*, St. Louis, 1918, i, 144-155.
A more intensive form of arsphenamine therapy.—*Am. J. Syph.*, St. Louis, 1918, ii, 778-779.
More contract surgeons (Letter).—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1184.
Duties of the dermatologist.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1989-1990.
Dermatology and the war.—*Med. & Surg.*, St. Louis, 1918, ii, 145-151.
- HILLER, ALMA, MOSENTHAL, H. O., and CLAUSEN, S. W.
The effect of diet on blood sugar in diabetes mellitus.—*Arch. Int. Med.*, Chicago, 1918, xli, 93-108.

HINMAN, F.

The management of surgical risk: a review of 100 kidney and prostate operations, and 50 cases of enlarged prostate not operated upon.—*Calif. State J. M.*, San Fran., 1918, xvi, 211-215.
A modification of Uitzmann's syringe for posterior urethral installations.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1297.

HINMAN, F., and LISSER, H.

Syphilis of the epididymis without involvement of the testicle: Report of case.—*Am. J. Syph.*, St. Louis, 1918, ii, 465-471.

HIRSCHFELDER, A. D.

The teaching of pharmacology.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 609-612.

HIRSCHFELDER, A. D., and CANTWELL, W.

Effects of some amino acids upon the excised segments of intestine.—*J. Pharmacol. & Exper. Therap.*, Balt., 1918, xl, 178.

HITZROT, J. M.

The effect of splenectomy on the normal individual and in certain pathological conditions.—*Ann. Surg.*, Phila., 1918, lxxvii, 540-559.
Myeloma of the clavicle.—*Ann. Surg.*, Phila., 1918, lxxvii, 92-94.

HOLMES, J. B.

Recent work in anatomy, physiology and pathology of childhood.—*Am. J. Dis. Child.*, Chicago, 1918, xv, 278-308.

HOOKER, D. R.

The veno-pressor mechanism.—*Am. J. Physiol.*, Balt., 1918, xlv, 591-598.

HOOKER, D. R., and MACHT, D. I.

Concerning the action of the iodide, bromide and nitrate ions on the respiratory center.—*J. Pharmacol. & Exper. Therap.*, 1918, xl, 63-67.

HOPKINS, J. G., and PARKEE, JULIA T.

The effect of injections of hemolytic streptococci on susceptible and insusceptible animals.—*J. Exper. M.*, Balt., 1918, xxvii, 1-26.

HOWARD, C. P.

Some of the medical lessons of the present war.—*J. Iowa State M. Soc.*, Clinton, 1918, viii, 352.

HOWARD, C. P., and INGVALDSEN, T.

The mineral metabolism of experimental surgery of the monkey.—*Univ. Iowa Monographs*, Studies in Med., 1918, i, 1-10.

HOWARD, C. P., and STEVENS, F. A.

The iron metabolism of hemochromatosis.—*Univ. Iowa Monographs*, Studies in Med., 1918, i, 1-17.

HOWELL, W. H.

The coagulation of blood.—*Harvey Lect.*, 1916-17, Phila. & Lond., 1918, 272-323.

HOWLAND, J., and MARRIOTT, W. M.

Acidosis.—*Penn. M. J.*, Athens, Pa., 1918, xxi, 429-436.
The influence of acid phosphate on the elimination of ammonia in the urine.—*Arch. Int. Med.*, Chicago, 1918, xxi, 477-482.
Observations upon the calcium content of the blood in infantile tetany and upon the effect of treatment by calcium.—*Quart. J. Med.*, Oxford, 1918, xl, 289-319.

HUNTER, G. L.

Anatomy, abnormalities, injuries and diseases of the ureter.—In: *Mod. Urol.* (Cahot), 8^e, Phila. & N. Y., 1918, ii, 245-311.
A rare type of bladder ulcer. Further notes, with a report of eighteen cases.—*Am. M. Ass.*, Chicago, 1918, lxx, 203-212.
Bladder ulcer of the bladder. Further notes on a rare type of bladder ulcer, with a report of twenty-five cases.—*Am. J. Obst.*, N. Y., 1918, lxxviii, 374-395.
The etiology of ureteral calculus.—*Surg. Gynec. & Obst.*, Chicago, 1918, xxvii, 252-270.

HURWITZ, S. H.

The value of renal functional studies in the prognosis and treatment of nephritis.—*Calif. State J. M.*, San Fran., 1918, xvi, 287-293.

HURWITZ, S. H., and FALCONER, E. H.

The value of Roentgen rays and benzene in the treatment of poly cythemia vera.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1143-1145.

HURWITZ, S. H., MEYER, K. F., and TAUSSIG, L.

Studies on the blood proteins. III. Abnormal globulin ratios in multiple immunity.—*J. Infect. Dis.*, Chicago, 1918, xxii, 1-27.

JACK, W. D., and BALLEUL, L. C.

The use of fascial transplants in war surgery.—*Ann. Surg.*, Phila., 1918, lxxvii, 1-4.

JANEWAY, T. C., RICHARDSON, H. B., and PARK, E. A.

Experiments on the vasoconstrictor action of blood serum.—*Arch. Int. Med.*, Chicago, 1918, xxi, 565-603.

KEIDEL, A.

Parasitology and serology of syphilis.—*Am. J. Syph.*, St. Louis, 1918, ii, 276-287. Also: *South. M. J.*, Birmingham, Ala., 1918, xl, 267-274.

KEIDEL, A., and ZIMMERMANN, E. L.

Tattooing and syphilis.—*Am. J. Syph.*, St. Louis, 1918, i, 83-96.

KEITH, N. M., and THOMSON, W. W. D.

War nephritis, a clinical, functional, and pathological study.—*Quart. J. Med.*, Oxford, 1918, xl, 229-266.

KELLY, H. A.

Fibroid tumors of the uterus treated with radium.—*Charlotte (N. C.) M. J.*, 1918, lxxvii, 135-137.
Fibroid tumors and radium.—*Virginia M. Month.*, Richmond, Va., 1918, xiv, 1-7.
Two hundred and ten fibroid tumors treated by radium.—*Tr. Am. Gynec. Soc.*, Phila., 1918, xviii.
Theology Caldwell Janeway, 1872-1917.—*Boston M. & S. J.*, 1918, cxxix, 597-599.
Joseph Price, 1853-1911.—*Boston M. & S. J.*, 1918, cxxix, 681-684.
John Herr Mosser, 1850-1912.—*Bost. M. & S. J.*, 1918, cxxix, 772.
Dr. Keen on medical research.—*Science*, N. Y. & Lancaster, Pa., 1918, n. s., xlvii, 419.

KEMPF, E. J.

Social and sexual behavior of monkeys with some comparable facts in human sexual behavior.—[Abstr.] *Am. J. Urol.*, N. Y., 1918, xlv, 82-86.

KING, J. T.

Auscultation of pulmonary apices in young men.—*Mil. Surg.*, Wash., 1918, xiii, 60-65.

KNOX, J. H. M.

America's debt to France.—*Am. J. Dis. Child.*, Chicago, 1918, xvi, 242-252.

KRAUSE, A. K.

Rest.—*Am. Rev. Tuberc.*, Balt., 1918, i, 680-682.
Elementary concepts of tuberculosis.—*Am. Rev. Tuberc.*, Balt., 1918, ii, 63-71.
Predisposition. (Editorial.)—*Am. Rev. Tuberc.*, Balt., 1918, ii, 43-48.
Tobacco smoke and pulmonary tuberculosis. (Editorial.)—*Am. Rev. Tuberc.*, Balt., 1918, ii, 99-105.
Antituberculosis measures.—*Am. Rev. Tuberc.*, Balt., 1918, ii, 637-653.
Essays on tuberculosis:
1. Before the tubercle bacillus.
2. Before Robert Koch.
3. Robert Koch.
4. The tubercle bacillus.
5. Infection: introductory considerations.
6. Sources of infection: Cochet's theory of dust infection.
7. Infection by inhalation: Flügge's theory of droplet infection.
8. Infection by ingestion: part one.
9. Infection by ingestion: part two: the first experiments.
10. Infection by ingestion: Part three: The occurrence of bovine bacilli in man.
11. Infection: special characteristics of tuberculous infection.
—*J. Outdoor Life*, N. Y., 1918, xv, 1-6; 30-41; 65-73; 86; 101-109; 120; 129-137; 163-169; 199-204.
—*J. Outdoor Life*, N. Y., 1918, xv, 225-230; 246-250; 269-275; 295-300.
—*J. Outdoor Life*, N. Y., 1918, xv, 327-329; 342-344; 363-367; 374.

LANGE, LINDA B.

The complement fixation test for tuberculosis.—*Am. Rev. Tuberc.*, Balt., 1918, ii, 541-545.

LAWRENCE, J. S.

A study of the aerobic bacteria found in wounds received on the battlefield of the Somme.—*Mil. Surg.*, Wash., 1918, xiii, 140-153.

LEVY, R. L.

The effect of thyroid secretion on the excitability of the endings of the cardiac vagus.—*Arch. Int. Med.*, Chicago, 1918, xxi, 263-268.

LEVY, R. L., and ALEXANDER, H. L.

The predisposition of streptococcus carriers to the complications of measles. Results of separation of carriers from non-carriers at a base hospital.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1827-1830.

LISSER, H.

Syphilis of the lung.—*Am. J. M. Sc.*, Phila., 1918, clv, 356-380.
The prevention of congenital syphilis by antileptic prenatal therapy.—*Calif. State J. M.*, San Fran., 1918, xvi, 384-388.
A note on the use of corpus luteum to prevent the painful breasts of menstruation.—*Endocrinology*, Glendale, Cal., 1918, ii, 12-15.

LISSER, H., and HINMAN, F.

Syphilis of the epididymis without involvement of the testicle: Report of case.—*Am. J. Syph.*, St. Louis, 1918, ii, 465-471.

LOEVENHART, A. S., BUNTING, C. H., and MARTIN, H. G.

The morphological changes in the tissues of the rabbit as a result of reduced oxidation.—*J. Exper. M.*, Balt., 1918, xxvii, 399-412.

LYMAN, D. R.

The control of the careless consumptive.—*Am. Rev. Tuberc.*, Balt., 1918, ii, 36-42.
Following up the discharged sanatorium patient.—*Am. Rev. Tuberc.*, Balt., 1918, ii, 615-621.

MACCALLUM, W. G.

Pathology of the epidemic streptococcal bronchopneumonia in the army camps.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 704-707.

MACCALLUM, W. G., and COLE, R.

Pneumonia at a base hospital.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1146-1156.

McCLURE, W. B., and SAUER, L. W.

Observations regarding the loss of water vapor through the skin in infants.—*Arch. Int. Med.*, Chicago, 1918, xxi, 428-430.

McCRAE, T.

Tuberculosis and the soldier.—*Am. Rev. Tuberc.*, Balt., 1918, ii, 372-379.

MACHT, D. I.

- Jewish food problems.—*Jewish Forum*, 1918, Nos. i, 1-2.
 A case of aspirin habit.—*Med. Rec.*, N. Y., 1918, xciv, 707.
 On the absorption of apomorphin and morphin through unusual channels.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1917-18, xv, 26-27.
 On the comparative absorptive power for drugs of the bladder and urethra (male).—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1917-18, xv, 45-46.
 On the relation of the chemical structure of the opium alkaloids to their effect on smooth muscle and on the discovery of a new therapeutic agent as a consequence thereof.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1918, xv, 63-66.
 On the relation between the chemical structure of the opium alkaloids and their physiological action on smooth muscle with a pharmacological and therapeutic study of some benzyl esters: I. On the relation of the chemical structure of the opium alkaloids to their action on smooth muscle. II. A pharmacological and therapeutic study of some benzyl esters.—*J. Pharmacol. & Exper. Therap.*, Balt., 1918, xi, 389-417, 419-446.
 On the absorption of drugs and poisons from the bladder and the urethra: I. Absorption of apomorphin and morphin. II. Absorption of various alkaloids, antiseptics, local anesthetics and salts.—*J. Urol.*, Balt., 1918, ii, 43-49; 211-226.
 On parotitis as a complication of influenza.—*Med. Rec.*, N. Y., 1918, xciv, 1117.

MACHT, D. I., and HOOKER, D. R.

- Concerning the action of the iodide, bromide and nitrate ions on the respiratory center.—*J. Pharmacol. & Exper. Therap.*, Balt., 1918, xi, 63-67.

MACHT, D. I., ISAACS, S., and GREENBERG, J. P.

- On the influence of some antiparetic and antiparetics on the field of vision.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1917-18, xv, 46-48.
 On the influence of some antiparetics on the neuro-muscular coordination test of "tapping".—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1917-18, xv, 61-62.

MAJOR, R. H.

- Importance of focal infection in diseases of obscure etiology. *Med. Herald*, St. Joseph, 1918, xxxvii, 59-163.
 Uremic ulceration of the intestine.—*J. Kansas M. Soc.*, Topeka, 1918, xviii, 136.
 A study of the Krukenberg tumor.—*Surg., Gynec. & Obst.*, Chicago, 1918, xxvii, 195-204.

MAJOR, R. H., and BLACK, D. R.

- A huge hemangioma of the liver associated with hemangiomata of the skull and bilateral cystic adrenals.—*Am. J. M. Sc.*, Phila., 1918, civi, 469-483.

MARRIOTT, W. M., and HOWLAND, J.

- The influence of acid phosphate on the elimination of ammonia in the urine.—*Arch. Int. Med.*, Chicago, 1918, xxii, 477-482.
 Acidosis.—*Penn. M. J.*, Athens, Pa., 1918, xxi, 429-436.
 Observations upon the calcium content of the blood in infantile tetany and upon the effect of treatment by calcium.—*Quart. J. Med.*, Oxford, 1918, xi, 289-319.

MARRIOTT, W. M., and SISSON, W. R.

- Variations in the lipid ("fat") content of the blood of infants under certain nutritional conditions.—*Am. J. Dis. Child.*, Chicago, 1918, xvi, 75-82.

MARSHALL, H. W.

- Structural deformities versus functional efficiencies as objects of treatments.—*Boston M. & S. J.*, 1918, clxxviii, 708-712.
 Revised ideas concerning foot defects and orthopedic footwear.—*Boston M. & S. J.*, 1918, clxxviii, 428-432.

MAXCY, K. F.

- Observations on the presence of the meningococcus in the blood.—*J. Infect. Dis.*, Chicago, 1918, xxiii, 470-474.

MAXCY, K. F., and BLACKFAN, K. D.

- The intraperitoneal injection of saline solution.—*Am. J. Dis. Child.*, Chicago, 1918, xv, 19-28.

MENDENHALL, DOROTHY R.

- Milk, the indispensable food for children.—U. S. Dept. Labor, Children's Bureau, Care of Children Ser. No. 4, Bureau Publ. No. 35, Wash., Gov't Printing Off., 1918.

MEYER, A.

- Modern views and propositions on enforced treatment of mental diseases.—*Maryland Psychiat. Q.*, Balt., 1918, vii, 37-58.
 The mental hygiene movement.—*Canad. M. Ass. J.*, Toronto, 1918, viii, 632-634.

MEYER, A. W.

- To Franklin Paine Mall, Ave Magister! *Johns Hopkins Alumni Mag.*, Balt., 1918, vi, 145.
 Some observations on megacytes in lymphatic tissues.—*Am. J. Anat.*, Balt., 1918, xciv, 91-104.
 Studies on hemal nodes: VIII. The absence of hemal nodes in the domestic pig.—*Am. J. Anat.*, Balt., 1918, xciv, 109-120.

MILLER, S. R., and BAETJER, W. A.

- Pollinosis or hay-fever: its specific treatment.—*South. M. J.*, Birmingham, Ala., 1918, xi, 341-345.
 Bence-Jones proteinuria; some observations on its occurrence, with particular reference to arthritis and hypertension.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 137-139.

MILLER, S. R., and BARKER, L. F.

- Perforating ulcer of the hard palate resembling tertiary syphilis.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 793-797.

MILLER, W. S.

- A study of the nerves and ganglia of the lung in a case of pulmonary tuberculosis.—*Am. Rev. Tuberc.*, Balt., 1917-18, i, 123-139.

MILLS, C. W., and HENDERSON, J. T.

- The effect of pulmonary tuberculosis on renal function.—*Am. Rev. Tuberc.*, Balt., 1917-18, i, 573-597.

MILLS, C. W., and FORSTER, A. M.

- The treatment of laryngeal tuberculosis by reflected condensed sunlight.—*Nat. Ass. Study & Prev. Tuberc.*, Tr., 1918, xiv.

MILLS, R. G.

- Japanese medical literature. Review of current periodicals by the staff of the research department, Severance Union Medical College, Seoul, Korea.—*China M. J.*, Shanghai, 1918, xxxii, 49-63; 256-267; 354-365; 462-473.
 An unusual case of double carcinoma with extreme resistance to one and death from the effects of the other.—*China M. J.*, Shanghai, 1918, xxxiii.

MILLS, R. G., LUDLOW, A. I., and VAN BUSKIRK, J. D.

- A simple method of water purification for itinerant missionaries and other travellers.—*China M. J.*, Shanghai, 1918, xxxii, 137-145.

MINOT, G. R.

- Pathologic hemorrhage. A group of cases illustrating this condition with a note on the early diagnosis of pernicious anemia.—*Med. Clin. N. Am.*, Phila., 1918, i, 1102-1124.

MINOT, G. R., and LOEB, R. F.

- An attempt to prevent influenza at Harvard College.—*Boston M. & S. J.*, 1918, clxxix, 665-669.

MORSE, A. H.

- Premature separation of the normally implanted placenta.—*Surg. Gynec. Obst.*, Chicago, 1918, xcvi, 133-138.

MORRIS, R. S., and FRIEDLANDER, A.

- The significance of presystolic thrill in the examination of soldiers.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 375-377.

MOSENTHAL, H. O.

- Renal function as measured by the elimination of fluids, salt and nitrogen, and the specific gravity of the urine. II. The effect of high, low and normal diets.—*Arch. Int. Med.*, Chicago, 1918, xxi, 770-804.
 War nephritis, by P. Ameuille. Transl. from the French by H. C. Mosenthal.—*J. Urol.*, Balt., 1918, ii, 51-106.

MOSENTHAL, H. O., and CLAUSEN, S. W.

- The maintenance diet in diabetes mellitus as determined by the nitrogen equilibrium.—*Arch. Int. Med.*, Chicago, 1918, xxi, 269-281.

MOSENTHAL, H. O., CLAUSEN, S. W., and HILLER, ALMA.

- The effect of diet on blood sugar in diabetes mellitus.—*Arch. Int. Med.*, Chicago, 1918, xxi, 93-108.

MOSENTHAL, H. O., and HARROP, G. A.

- The comparative food value of protein, fat and alcohol in diabetes mellitus as measured by the nitrogen equilibrium.—*Arch. Int. Med.*, Chicago, 1918, xxi, 750-758.

NEYMANN, C. A., and BURROWS, M. T.

- Studies on the metabolism of cells in vitro. The toxicity of dipeptides for embryonic chicken cells.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1918, xv, 138-139.

NIXON, P. I.

- Inflammatory tumors of the abdomen.—*Ann. Surg.*, Phila., 1918, lxxvii, 306-311.

NOVAK, E.

- Infantilism and other hypoplastic conditions of the uterus.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 1101-1107.

NUTTALL, G. H. F.

- The pathological effects of Phthirus pubis.—*Parasitology*, London, 1918, x, 375-379.
 The biology of Phthirus pubis.—*Parasitology*, Lond., 1918, x, 383-405.

NUTTING, M. ADELAIDE.

- War-time problems of the nursing profession.—*Johns Hopkins Nurses Alumni Mag.*, Balt., 1918, xvii, 93-100.

OPIE, E. L., BAETJER, W. [et al].

- Report on progress of trench fever investigations. Trench Fever Commission of Medical Research Committee, American Red Cross.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1597-1598.

OPIE, E. L., and WORUS, R. E.

- Elephantiasis: report of a case.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 987.

OSLER, SIR W.

- Typhoid spine. *Bull. Canadian Army M. Corps*, 1918, i, 78-79.
 Graduated exercise in prognosis.—*Lancet*, Lond., 1918, i, 231.
 The primary examination for the F. R. C. S. Eng.: an appeal to the President of the Royal College of Surgeons.—*Lancet*, Lond., 1918, i, 715.
 Medicine in America (Speech to University Extension Students, summer meeting at Cambridge).—*The Hospital*, Lond., 1918, lxxv, 433.

PARFITT, C. D.

- The utility of artificial pneumothorax in the treatment of phthisis.—*Canada Lancet*, Toronto, 1918-19, iii, 64-72.

PARK, E. A., JANEWAY, T. C., and RICHARDSON, H. B.

- Experiments on the vasoconstrictor action of blood serum.—*Arch. Int. Med.*, Chicago, 1918, xxi, 565-603.

PATON, S.

- Effects of low oxygen pressure on the personality of the aviator.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 1399-1400.

PEABODY, F. W.

Cardiac dyspnea.—*Am. J. M. Sc.*, Phila., 1918, clv, 100-117.
Cardiac dyspnea.—*Harvey Lect.*, 1916-17, Phila. & Lond., 1918, 248-251.

PEABODY, F. W., CLOUGH, H. A., STURGIS, C. C. [et al.].

Effects of the injection of epinephrin in soldiers with "irritable heart". Preliminary report.—*J. Am. M. Ass.*, Chicago, 1918, lxxv, 1942-1943.

PEARCE, LOUISE, and BROWN, W. H.

Experimental lymphomatosis as application in chemotherapeutic investigations.—*J. Exper. M., Balt.*, 1918, xxviii, 109-117.

PENROSE, C. A.

Experience in camp and field exercises.—*Johns Hopkins Alumni Mag.*, Balt., 1918, vi, 358-355.

PLAGGEMEYER, H. W.

Radical treatment for vesicovaginal fistula.—*Grace Hosp. Bull.*, Detroit, 1917-18, II, 17-19.

QUINBY, W. C.

Anatomy and physiology of the kidney. In: *Mod. Urol.* (Cahot), S. B. and N. Y., 1918, p. 312-336.
Anatomy and physiology of the prostate and seminal vesicles. In: *Mod. Urol.* (Cahot), S. B. and N. Y., 1918, p. 541-552.
The treatment of genital tuberculosis in the male.—*J. Am. M. Ass.*, Chicago, 1918, lxxv, 1790-1796.

RICHARDSON, E. H.

Note on saphenous varix simulating a femoral hernia.—*Ann. Surg.*, Phila., 1918, lxxv, 471-472.

Incision of the uterus several inches in women.—*South. M. J.*, Birmingham, Ala., 1918, xl, 130-144.
The effect of hysterectomy upon ovarian function.—*Tr. Am. Gynec. Soc.*, Phila., 1918, lxviii.

RICHARDSON, H. B., JANEWAY, T. C., and PARK, E. A.

Experiments on the vasoconstrictor action of blood serum.—*Arch. Int. Med.*, Chicago, 1918, xxi, 565-603.

ROSEN, R., DAVIS, E. G., and WHITE, E. C.

Urinary antiseptics. The secretion of antiseptic urine following the intravenous administration of an organo-mercurial phosphate derivative.—*J. Urol.*, Balt., 1918, II, 277-307.

ROUS, P.

Method for intravenous injection of guinea pigs.—*J. Exper. M., Balt.*, 1918, xxviii, 459-462.

Urinary siderosis. Hemosiderin granules in the urine as an aid in the diagnosis of pernicious anemia, hemochromatosis, and other diseases causing siderosis of the kidney.—*J. Exper. M., Balt.*, 1918, xxviii, 645-659.

ROUS, P., and OLIVER, J.

Experimental hemochromatosis.—*J. Exper. M., Balt.*, 1918, xxviii, 629-634.

ROUS, P., and ROBERTSON, O. H.

Free antigen and antibody circulating together in large amounts hemagglutinin and agglutinin in the blood of transfused rabbits.—*J. Urol.*, Balt., 1918, xxviii, 509-517.
Autohemagglutination experimentally induced by the repeated withdrawal of blood.—*J. Exper. M., Balt.*, 1918, xxviii, 563-568.

ROUS, P., and WILSON, G. W.

Fluid substitutes for transfusion after hemorrhage; first communication.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 219-222.

ROWNTREE, L. G.

Syphilis in its medical, its general, and its sociological aspects.—*Therap. Gaz.*, Detroit, 1918, n. s., xxxviii, 222-225.

ROWNTREE, L. G., and BARKER, L. F.

A report of a case of myrtle poisoning with comments upon the toxicity of eucalyptus oil and myrtle in human beings and in animals.—*Tr. Ass. Am. Physicians*, Phila., 1918, xxxiii.

RUSHMORE, S.

Progress in gynecology.—*Boston M. & S. J.*, 1918, clxxviii, 533-539.

SABIN, FLORENCE R.

Franklin Paine Mall: a review of his scientific achievement.—*Science*, N. Y. & Lancaster, Pa., 1918, n. s., xlvii, 254-261.

SAMPSON, J. A.

The escape of foreign material from the uterine cavity into the uterine veins.—*Am. J. Obst.*, N. Y., 1918, lxxviii, 161-175.

SELLARDS, A. W.

Alcoholism and associated conditions.—*Med. Clin. N. Am.*, Phila., 1918, p. 1125-1141.
Experimental studies of alcoholism with special reference to the chronic action of dilute sodium hydroxide on certain races of the guinea pig.—*J. Am. M. Ass.*, Chicago, 1918, lxxv, 1942-1943.
The treatment of alcoholism.—*J. Pharmacol. & Exper. Therap.*, Balt., 1918, xl, 331.

SELLARDS, A. W., SPOONER, L. H., and WYMAN, J. H.

Study of the effect of the administration of the guinea pig.—*J. Am. M. Ass.*, Chicago, 1918, lxxv, 1942-1943.

SHARPE, W.

Diagnosis and treatment of brain injuries with or without fracture of the skull.—*Am. J. Surg.*, N. Y., 1918, xxxii, 109-114.

The operative treatment of trifacial neuralgia.—*Ann. Surg.*, Phila., 1918, lxxv, 371-378.

Recent advances in neurological surgery and especially in the diagnosis and treatment of brain injuries.—*J. Am. M. Ass.*, Chicago, 1918, lxxv, 1942-1943.

Operative treatment in selected cases of chronic peripheral facial paralysis.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1354-1357.

Recent advances in the surgery of the brain and spinal cord.—*Journal-Lancet*, Minneapolis, 1918, xxxvii, 313-318.

Fractures of the skull: the resulting intracranial pathology and the treatment.—*Med. & Surg.*, St. Louis, Mo., 1918, II, 319-333.

Observations regarding neurological surgery, and especially the diagnosis and treatment of brain injuries.—*J. Tenn. M. Ass.*, Nashville, 1918, IX, 67-75.

Observations regarding the diagnosis and treatment of brain injuries with or without a fracture of the skull.—*Minnesota M.*, 1918, p. 283-294.

SIMON, C. E.

A manual of clinical diagnosis by means of laboratory methods.—9 ed., Phila. & Lond., 1918, Lea & Febiger, 851, p. 80.

The probable association of amino-aciduria with Bence-Jones proteinuria.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 224.

SISSON, W. R.

A critical review of intestinal bacteriology in relation to certain diarrheas of infants.—*Boston M. & S. J.*, 1918, clxxviii, 492-498.

SISSON, W. R., and MARRIOTT, W. M.

Variations in the lipid ("fat") content of the blood of infants under certain nutritional conditions.—*Am. J. Dia. Child.*, Chicago, 1918, xvi, 75-82.

SLADEN, F. J., and FRIEDLANDER, A. [et al.].

The epidemic of influenza at Camp Sherman, Ohio.—*J. Am. M. Ass.*, Chicago, 1918, lxxv, 1652-1656.

SLEMONS, J. M.

The significance of fever at the time of labor.—*Am. J. Obst.*, N. Y., 1918, lxxviii, 321-328.

Analysis of the blood in clamps and allied hemorrhages.—*Am. J. Obst.*, N. Y., 1918, lxxvii, 797-806.

SMITH, W. H.

How nurses are meeting the present needs.—*Am. J. Nursing*, Rochester, N. Y., 1917-1918, xviii, 979-989.

The civil hospital and its duties in war time. [Abstr.].—*Trained Nurse* [etc.], N. Y., 1918, ix, 13-15.

Medical aspects of the war.—*Johns Hopkins Alumni Mag.*, Balt., 1918, vi, 348-367.

Some aspects of the program of the medical department of the army and their effect on civil hospitals.—*Mod. Hosp.*, St. Louis, 1918, xi, 334-336.

SPERRY, J. A.

Results following operative treatment of pelvic inflammatory disease in the Stanford University Clinic.—*Calif. State J. M.*, San Francisco, 1918, xvi, 388-390.

Vertical disease control by Board of Health of San Francisco.—*Calif. State J. M.*, San Francisco, 1918, xvi, 129-135.

STEVENS, A. R., and PETERS, J. P., Jr.

A study in war nephritis: a new condition associated with hemorrhages in the bladder wall and urinary symptoms: preliminary report.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1760-1763.

STRONG, R. P.

Etiology and method of transmission of trench fever.—*Bull. Acad. de Med. Par.*, 1918, 3, lx.

STRONG, R. P., SWIFT, H. F. [et al.].

Trench fever. Report of Commission Medical Research Committee, American Red Cross. [London], 1918, Oxford University Press, 446, p.

Report on progress of trench fever investigations. Trench Fever Commission of Medical Research Committee, American Red Cross.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 1597-1598.

Report on progress of trench fever investigations of Trench Fever Commission of Medical Research Committee, American Red Cross.—*Med. Bull. Am.*, 1918, p. 748-749.

STROUSE, S.

Juvenile diabetes in twins, the Karel treatment of edema. The importance of details in the treatment of angina pectoris.—*Med. Clin. N. Am.*, Phila., 1917-18, I, 1241-1259.

STROUSE, S., and BLOCH, L.

Nutrition in the treatment of angina pectoris.—*Med. Clin. N. Am.*, Phila., 1918, lxxv, 1569-1571.

THEOBALD, S.

Chief function of oblique muscles of the neck.—*Am. J. Surg.*, Phila., 1918, xii, 57-59.

VORSTER, C., and MARRIOTT, W. M.

Phosphorus as an indicator of the vitamin content of food products.—*Pub. Health Rep.*, Wash., 1918, xxxiii, 941-947.

WARFIELD, L. M.

Chronic endocarditis without acute onset.—*J. Am. M. Ass.*, Chicago, 1918, lxxv, 1942-1943.

WARFIELD, L. M., and MARRIOTT, W. M.

The etiology of arterio-sclerosis.—*J. Am. M. Ass.*, Chicago, 1918, lxxv, 1942-1943.

WARFIELD, L. M., and MARRIOTT, W. M.

The development of the seminal vesicles in man.—*Ann. Surg.*, Phila., 1918, lxxv, 106-102.

WARFIELD, L. M., and MARRIOTT, W. M.

Studies on irritable heart: preliminary report.—*J. Am. M. Ass.*, Chicago, 1918, lxxv, 1942-1943.

WARFIELD, L. M.

The development of the seminal vesicles in man.—*Ann. Surg.*, Phila., 1918, lxxv, 106-102.

- The human seminal vesicles at birth, with observations on their fetal development.—*Ann. Surg.*, Phila., 1918, lxxvii, 416-419. Also: *Tr. Sect. Genito-Urin. Dis. Am. M. Ass.*, Chicago, 1918, lxi.
- The essentials of success in prostatic surgery.—*Canad. M. Ass. J.*, Toronto, 1918, viii, 327-332.
- The place of intraspiral therapy in urology.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 296-300.
- The developmental stages of the human seminal vesicles.—*J. Urol.*, Balt., 1918, ii, 129-139.
- The structure of the verumontanum—a study of the origin and development of its inherent glandular elements.—*J. Urol.*, Balt., 1918, ii, 337-351.
- WATTS, S. H.
Acute and subacute pancreatitis. Report of seven cases.—*Ann. Surg.*, Phila., 1918, lxxvii, 278-292.
- The treatment of certain forms of subacute pancreatitis.—*Surg., Gynec. & Obst.*, Chicago, 1918, xxvii, 286-288.
- WEBB, C. W.
Surgical treatment of goiter.—*N. York State J. M.*, N. Y., 1918, xxvii, 272-278. Also: *Clifton Med. Bull.*, Clifton Springs, 1918, 12-18.
- WELCH, W. H.
Letter to S. Adolphus Knopf, M. D. An introduction to "What the American soldier now fighting in France should know about tuberculosis," by S. Adolphus Knopf.—*J. Outdoor Life*, N. Y., 1918, xv, 14.
- WHIPPLE, G. H., and COOK, J. V.
Protease intoxications and injury of body protein. IV. The metabolism of dogs with sterile abscesses, pancreatitis, and pleuritis. V. The increase in non-protein nitrogen of the blood in acute inflammatory processes and acute intoxications.—*J. Exper. M.*, Balt., 1918, xxviii, 223-241; 243-252.
- WHIPPLE, G. H., and VAN SLYKE, D. D.
Protease intoxications and injury of body protein. III. Toxic protein catabolism and its influence upon the non-protein nitrogen partition of the blood.—*J. Exper. M.*, Balt., 1918, xxviii, 213-221.
- WHITE, E. C., and DAVIS, E. G.
Urinary antiseptics. The secretion of antiseptic urine following the intravenous administration of acridavine and proflavine preliminary report.—*J. Urol.*, Balt., 1918, ii, 299-307.
- WHITE, E. C., DAVIS, E. G., and ROSEN, R.
Urinary antiseptics. The secretion of antiseptic urine following the intravenous administration of an organo-mercury phthalein derivative.—*J. Urol.*, Balt., 1918, ii, 277-307.
- WILLIAMS, J. W.
A consideration of some of the anatomical factors concerned in the production of deformed pelvis.—*Am. J. Obst.*, N. Y., 1918, lxxvii, 714-758.
- WOLFSOHN, J. M.
The predisposing factors of war psychoneuroses.—*J. Am. M. Ass.*, Chicago, 1918, lxx, 303-308. Also: *Lancet*, Lond., 1918, i, 177-180.
- The treatment of hysteria: successful results of a rapid re-education method.—*J. Am. M. Ass.*, Chicago, 1918, lxxi, 2057-2062.
- WOOLLEY, P. G.
Three cases which illustrate the consequences of coronary lesions.—*J. Lab. & Clin. M.*, St. Louis, 1917-18, iii, 192-198.
- Meningitis at Camp Greene.—*J. Lab. & Clin. M.*, St. Louis, 1917-18, iii, 409-412.
- Three cases of parietal aortic thrombosis. *J. Lab. & Clin. Med.*, St. Louis, Mo., 1917-18, iii, 539-547.
- Convulsions. (Editorial).—*J. Lab. & Clin. M.*, St. Louis, 1917-18, iii, 719-720.
- YATES, J. L.
Surgical methods in the treatment of malign affections of superficial lymphatic tissue.—*Surg., Gynec. & Obst.*, Chicago, 1918, xxvii, 156-162.
- Observations of a Wisconsin medical officer in France.—*Wisconsin M. J.*, Milwaukee, 1917-18, xvi, 476-477.
- YOUNG, H. H.
Cancer of the prostate.—In: *Mod. Urol.* (Cabot), 8th, Phila. and N. Y., 1918, i, 657-719.
- Sarcoma of the prostate.—In: *Mod. Urol.* (Cabot), 8th, Phila. and N. Y., 1918, i, 720-722.
- Calculus disease of the prostate.—In: *Mod. Urol.* (Cabot), 8th, Phila. and N. Y., 1918, i, 723-724.
- The employment of the high frequency current for the extraction of calculi incarcerated in the lower end of the ureter.—*J. Urol.*, Balt., 1918, ii, 35-38.
- A new operation for epispadias.—*J. Urol.*, Balt., 1918, ii, 237-251.
- Recent progress in the treatment of cancer of the prostate, seminal vesicles and bladder.—*South. M. J.*, Birmingham, Ala., 1918, xi, 120-129.
- Excision of vesical diverticula after intravesical invagination by suction; a new method.—*Surg., Gynec. & Obst.*, Chicago, 1918, xxvi, 125-132.
- Presentation of a radical operation for tuberculosis of the seminal tract.—*Surg., Gynec. & Obst.*, Chicago, 1918, xxvi, 375-384.
- Changes in trigone due to tuberculosis of kidney, ureter, and bladder. Bridge formation and floating trigone.—*Surg., Gynec. & Obst.*, Chicago, 1918, xxvi, 608-615.
- YOUNG, H. H., and DAVIS, E. G.
The surgery of the double kidney. Report of a case of resection of upper segment for calculus pyonephrosis.—*Surg., Gynec. & Obst.*, Chicago, 1918, xxvii, 1-13.
- ZIMMERMAN, E. L., and KEIDEL, A.
Tattooing and syphilis.—*Am. J. Syph.*, St. Louis, 1918, i, 83-96.

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ANTITUBERCULOSIS MEASURES¹

By ALLEN K. KRAUSE

Scared and battered as few other epochs of the world the twentieth century is only completing its childhood; and, let us hope that its survival from maladies that only yesterday seemed mortal presages a sturdy and productive maturity and a mellow senescence. Were we required to characterize with a word the point of view,—the spirit,—that animated most of us with the birth of 1900 I believe that not a few would select "comfortable." Comfortable we were and comfortable we expected to remain. During the last two decades of the nineteenth century the conveniences of life had developed and multiplied to such an extent that what had once been the luxuries of the opulent, or had even been beyond their reach, had become everyman's necessities. And as the twentieth century added to its years, as its step became more certain and it began to reach out and grope for guidance into the mists of the illimitable future, it did so with far steadier hand perhaps than had ever drawn along any of the children of Time. For were we not at last masters of our environment? Had not the curse of our first parents lost most of its sting? Labor we must, yes,—and we must

look forward ever to continue to labor. But we were to labor in a world such as our progenitors never dreamed of. Electricity now carried us to our shops. To press a button was to light our way into our homes when we returned at night. A turn of the switch in our living room and heat began to radiate through the house. Every home boasted of arrangements that made for cleanliness, and therefore health,—arrangements that were not available for even the regents of man of fifty years ago. Almost everyone of us could sit in his easy chair and talk with his friend at the other end of the city. From our old ashes we made us dyes of a variety and beauty that far surpassed those of the plants and beetles of the sleepy Orient, and we were led to develop our taste for ornament and for clothes; and possessing more than a necessity of clothes we were led further toward cleanliness and health.

Kindred examples might be multiplied at length. But what we would emphasize is that, if the tremendous increase and widespread distribution of comforts and conveniences made for any one specific thing, they promoted leisure—leisure, which in its enormous aggregate must have a not inconsiderable influence on the mass-manifestation of many human diseases, and particularly on such maladies that owe not a little to stress and strain to bring them to light. Among

¹An address delivered under the title, "Some Aspects of the Problem," at the general meeting of the New Jersey Joint Conference on Tuberculosis, Perth Amboy, New Jersey, November 23, 1918.

such diseases tuberculosis undoubtedly takes its place. It is not my intention to discuss this phase of the situation to-day, except perhaps to refer to it occasionally in the course of my address. But before leaving it entirely I cannot refrain from calling attention to the large part that customs and modes of life, operating over long periods, changing slowly, almost imperceptibly and yet very definitely, if we consider sharply outlined economic epochs, must play in influencing the morbidity and mortality statistics of a disease like tuberculosis. It will not hamper the student of tuberculosis if he is also familiar with the history of civilization.

By 1900 we had achieved a degree of physical comfort that was before unthought of and I do not think it an exaggeration to venture that we were approaching a comparatively stable state of comfortableness in our mental concepts. In morals? Well, every age is certain of the absolute rectitude of its moral aims, even though a comparative reading of Marcus Aurelius, of Machiavelli, of Bunyan, of Pepys, and of Wesley, leaves the infant mind a bit confused. In politics? At no time were we white men more certain of our God-given function of "benevolent assimilators" than in 1900. In economics? Capital, and we are all capitalists at heart, was never surer of its complete altruism,—things moved only because we of the dollars at great sacrifice hazarded our dollars to put the wheels in motion and save those of no-dollars from starvation. In applied science? Man had embalmed the human voice to resurrect it at will. He had begun to fly in the air and to sail his craft in the depths of the ocean. He was building cloud-piercing edifices to house a small city's people in a block. He was recording actual movement and actual colors in snap-taken pictures. And so on. Man could do anything. In medicine? Deep-lying structure revealed on a photographic plate; the disabilities of the human heart transcribed in peaks and waves on a film; the provocative causes of hitherto obscure infections discovered by the dozens; totally new and unfamiliar conflicts brought to light in the humors of the body;—all these and many more achievements accumulated to convince us of our mastery over the forces of Nature and to give us a comfortable sense of security as we faced the future.

And tuberculosis? Tuberculosis also caught something of the universal and contagious complacency. Becoming enthusiastic because of several remarkable discoveries made in rapid succession we began to make claims. Made bold by unexpected successes we began to predict. We could cure tuberculosis. We knew its cause—the tubercle bacillus. We were also sure of how the tubercle bacillus came to us. We could, therefore, choke it off at the source and prevent tuberculosis. Indeed, so flushed were we in the first days of our new knowledge that we set the date for the disappearance of tuberculosis, and few of us are so young that we cannot remember the banners that flaunted, "No tuberculosis by 1915!" Unmindful of the many disappointments of the past, careless of the one outstanding fact that is so familiar to the student of tuberculosis, namely, that almost every new discovery, almost every penetrating ray of light, once its full significance was appreciated,

had never failed to indicate how much more complex was our problem than we had imagined, we pressed boldly on and made up our antituberculosis program.

This program was simple and it was direct. Based on the several plain facts that I have just outlined it was thoroughly logical and understandable. It is familiar to you all and may be summed up in a few words: institutions for the sick, the detection of disease at its very beginning, the control of the sources of infection.

Has it worked? I am told almost daily that it has not. But I always feel that the man who asserts that it has been a total failure and that it has contributed nothing to the salvation of the race is speaking altogether outside the facts. I know many men alive and highly productive to-day, who had the good fortune to become consumptive in the early nineteen-hundreds rather than in the eighteen-seventies. Thirty years before they would have been doomed to death and most of them would have died. I also know many "trained" consumptives who have fought their disease to a successful issue, and who have done this with their healthy babies around them, yet who fifty years ago would have sent many of these babies to scrofulosis and to death, and passed the blame therefor to their inherited taint. There can be no doubt that our program of control and our vulgarization of information have saved countless human lives and have prolonged ten times more. They have thus contributed tremendously to the potential and actual wealth of the world and have just as surely paid back to the people every penny they have ever received from them. A week's "sociological" inquiry will convince any unprejudiced person of these facts and should be sufficient to silence any destructive critic of the organized antituberculosis movement. But criticism there will remain and criticism there must remain if our work is to keep from stagnating and if our methods are to be kept so elastic that they can take advantage of the newer concepts that fresh contributions to knowledge are continually introducing.

Thoroughly convinced that the organized antituberculosis movement has exerted a tremendously salutary effect and just as certain that every man who is interested in any way whatever in the conquest of tuberculosis should wholeheartedly and unselfishly work toward a common end through one organized body, I nevertheless do not consider it conclusively proved that our organizations have always made full use of the more advanced knowledge of the day or that they have adopted all this newer information to themselves and applied it in all its implications and ramifications, no matter where these led. A certain fixity and non-development of the original plans, first bruited about the beginning of the century, have more than once impressed me. These plans, as I have said, were comparatively simple and direct. Few will disagree that they laid an overwhelming emphasis on the dangers of infection and on the necessity of paying attention to the sources of infection. In other words, they only followed the leading thought of the day, which was the outgrowth of the tremendous bacteriological bias that Koch and his followers saddled upon preventive medicine. They were formulated at a time when com-

mon opinion held that tuberculous infection and manifest tuberculosis in an adult were almost simultaneous occurrences. And if this appreciation of the tuberculosis situation had been a true one I believe that as a public health body our National Tuberculosis Association would have made far more progress in combating the disease than the steady strides it has already taken against a problem of almost incredible difficulty.

Our awakening began almost so gently that most of us refused to be stirred up. We may date the dawn of this new day to the Pirquet test. This simple manoeuvre, innocently put forward to aid us in diagnosis, to detect the consumptive even before he is aware of impending trouble, did not fulfill its original purpose. It did not point out who were tuberculous enough to be treated and who were not; and viewed from this angle it was a failure and exhibited a striking parallel to the fate of Koch's original attempts at the prevention and cure of tuberculosis. But never did a failure lead to more significant results! After several years,—after much grist had gone through the mill, it was found that the Pirquet test and all that it may mean had taught us many things that most of us would not have believed a decade before. Indeed, so multi-form and far-reaching are its implications that it is my own opinion that with Laennec's promulgation of the unity of phthisis, Villemin's discovery of the infectiousness of tubercle and Koch's revelation of the bacillus, it makes up the quartet of really great episodes in the history of tuberculosis. And in some respects I consider the era of ideas—ideas, many of which are still relatively embryonic and formless—that it ushered in as the greatest of all.

It made absolutely certain what a very few sturdy souls had previously suggested and what still fewer admitted, namely, that the generality of mankind that lives in close association with its fellows harbors the tubercle bacillus; that is, that most of us become infected comparatively early in life. Try to think now of all the implications that this one bare fact conveys. What a vista of the ubiquity of the tubercle bacillus it at once opens up,—a ubiquity such as even the early bacillus hunters from Koch to Flügge never even dreamed of! Where then shall we begin in our search and control of sources of infection? Why, with the man of "positive" sputum, of course. Granted;—and that too would be relatively easy; but where shall we go next? Why to the manifestly ill who may not be emitting bacilli. Let us go even further and refine our diagnostic methods and attempt to ferret out those who are not yet ill but who are about to become ill. We won't quarrel over whether this is possible or not: we shall set out to do it. Yes, and where then?—for we have thus far accounted for only the veriest fraction of the human race that is carrying around tubercle bacilli.

But,—you protest,—what difference does it make if nine-tenths of the harborers of tubercle bacilli, all healthy men, do carry with them the seeds of consumption? They are "safe" men. They are well and are not distributing bacilli among their neighbors.

Yes, they are "safe." But they are "safe" only so long as they are "safe" and who is there anywhere so endowed that he can detect the moment, the day, the month, aye, in some cases the year, that they pass from being "safe" neighbors to a menace? And in this period of dawning disease, this indefinite time of diagnostic uncertainty before the patient seeks medical advice, how many cycles of infection, think you, can the patient initiate? It has always been my impression that by the time a very average and a very large number of us come to our physician because of our tired feeling, or our cough, or our lack of endurance, we have already fairly thoroughly tuberculized most of those who move within our range of intimate contact.

The Pirquet test gives us a method to make epidemiological studies such as is possessed by the students of no other disease. Equipped with it and its modifications we can roam the world and make observations on man and animals everywhere and, with an error that is surely less than ten per cent, detect who is tuberculous and who is not. And when we observe infection among the very young, whose voluntary range of contact is quite limited, we should more than once be led to the detection of previously unsuspected sources. Epidemiological studies have been made, but all have been too limited and too sporadic. And we await the day when the state, or men of vision and large resources, shall make it possible for us to have ideas that are definite and well grounded because they are based on sufficiently broad observations. It has just taken billions to still the voice of autocracy and brutishness, and mankind has gladly given up its billions. Yet the voice of Benedict Spinoza, that "God-intoxicated man," was stilled by the tubercle bacillus, and we go stumbling along in our search for truth for want of the thousands to lay bare the tricks of the eternal enemy of all mankind.

How significant becomes what the Pirquet test now teaches us! If most of us harbor the tubercle bacillus and if at the same time but a small percentage of us ever fall sick with tuberculosis then nothing can be more certain than that the development of manifest disease, the efflorescence of a "safe" man into a menace, depends not so much upon the mere presence in us of the seed,—in other words, upon infection,—as upon some other factor or factors that enter into our experience. Not all these factors are by any means familiar to us; indeed, we probably are acquainted with very few of them specifically. But I do not think that we generalize too rashly, if we are not too "scientific" to refuse to learn from clinical experience that the factors determining the development of manifest tuberculosis are attributable to non-specific bodily effects that are brought about by what we may in general call "strain." Here we might classify the circulatory changes that are set up around old, unknown, and quiescent foci by such events, as pregnancy and labor, intercurrent disease, sudden intense or prolonged and more moderate physical effort, emotions such as anger or worry, abnormal habits or dissipation. Though its *modus operandi* is disputed, most men to-day agree that strain is an all-important factor in bringing tuberculosis into the realm of consciousness; and, if this

be granted, it must be equally true that its opposite, that is, relief or comparative relief from strain, will operate toward keeping quiescent tubercle in abeyance. It must therefore be perfectly certain that anything that leads to an amelioration of the general habits and conditions of life of masses or classes of people will work towards a subsidence of tuberculosis, epidemiologically speaking. And you will at once catch the drift of my remarks at the opening of this address that in appreciating the significance of the ups and downs of tuberculosis as a folk-disease we must also have some comprehension of the civilization of a people at any particular period that may be under consideration.

Our statistics, particularly those of the earlier decades, are anything but satisfactory and complete. Nevertheless they bring out one thing clearly. This is, that the tuberculosis mortality rate began to decline in practically every country, that was advancing industrially and was therefore increasing in wealth, as early as 1850 and for perhaps ten or twenty years before. This, remember, was thirty years before the discovery of the bacillus and when the disease was universally regarded as having a diathetic basis. In other words, tuberculosis began to abate its terrors before man intentionally applied a single measure to combat it. This fact must be familiar to you all and I shall not go into further detail concerning it. Personally, I can see only one reason for it, and this is the gradual bettering of the conditions of labor and living of the mass of the people that was ushered in markedly shortly before the middle of the last century and took on a tremendously accelerated impetus after 1880 and proceeded at an ever-progressing rate with only one or two brief interruptions (from 1893 to 1897 and in 1907) until the release of Armageddon in 1914.

Public health men have on occasion not been slow to seize upon this phenomenon and to throw it into the teeth of our antituberculosis boosters and boasters that figures showed that our own efforts had contributed nothing to a lessening of the greatest of all plagues but that this was brought about by forces that were intangible and over which we had no control. But truth is, that to speak thus is to argue, let us not say unfairly, yet nevertheless on a pinpoint. Such an assertion can be made in return like a boomerang upon the declarant. And, if we wished to draw comparisons and take a broader stand on the matter of infectious diseases in general, then following out the same line of argument, we should come dangerously close to a negation of the effect of public health work in general.

If we examine vital statistics we find that of the infectious diseases a decline in the death rate that began before what we may call the bacteriological era was not confined to tuberculosis alone. This is true of a number of diseases that we may call endemic in this part of the world,—of scarlet fever, of measles, of whooping cough, and of the enteric infections. We do not know the provocative causes of scarlet fever and measles, and cannot therefore combat them by specific measures. Yet scarlet fever has shown a marked decline, both in incidence and malignity, since about 1870. It must be obvious

that as the habits and modes of living of a population change there must be many balancing and opposing forces set in motion which make both for and against the occurrence of infectious diseases. On the one hand, we should expect that the enormously accelerated condensation of population and the unexampled development of the means of communication that have been going on in the United States during the last thirty years would, if they were unopposed by contrary factors, favor the spread of many infections. But against such forces we may put the high development of home and office and factory sanitation, the better and more equable house heating brought about by central heating systems; the tremendously increased interest in out-door play and sports, the reduction of the hours of labor, the more general enjoyment of vacations,—in short, anything and everything that contribute to the amelioration of social and domestic life.

We now take our enormous office buildings as a matter of course. We have seen architects erect the impossible and we have long passed the time when anything that is built can elicit an expression of amazement from us. Yet we seldom stop to think that, even though we were in possession of all the secrets of the assembling of structural steel and even though we could install our present-day elevators, it would be absolutely impossible to use these great buildings, to bring together myriads upon myriads of people on the ground-space of an acre, if we could give them no better sanitary appliances than those that were in vogue as recently as thirty years ago. Our great buildings depend just as much for their erection on latter-day plumbing as they do upon the development of the elevator and the structural steel industry. And when we assemble people together as we do to-day, we are doing this under conditions that, as regards many infectious diseases, are relatively healthful compared with those that obtained only a few decades ago; and these physical conditions originated not in the minds of sanitarians and public health officials, but in that greatest of all stimuli for the betterment of man,—industrial ambition in its quest for wealth.

It must also be self-evident that as a community like that of Manhattan Island, in its necessity for growth and expansion, reclaimed and built up the vacant stretches and waste areas of land and erected buildings upon these, it unconsciously, with no thought whatever of public hygiene, brought about conditions that were unfavorable to the development of several infections. Malaria would be one of these; endemic typhoid fever, another. We might go on and develop this phase of the subject indefinitely. But I have already taken up perhaps too much of your time with it; and I have brought it in to illustrate that not all betterment of health conditions need be due to the intentional efforts of sanitarians, and to give point to what I feel, namely, that the public health official and "scientific" investigator, who now and again calls upon us to demonstrate mathematically the net results of our efforts and who seems inclined to dislocate credit from us to other broad and more or less intangible forces, had better analyze honestly just how many endemic infections he

has by *intentional intervention and by this alone*, diminished or subdued.

I am conscious of the enormous part that public health has played in making our residence on earth livable. As an outsider, I have always been proud of what our more enlightened and untrammelled executives have sought to do and have actually accomplished. But I also feel very strongly that, as a body and as an arm of the health service, our own National Association has never stood second to any in tangible results, that it has had as much definite information at its command as is at hand to combat any contact infection, that in the main it has used this well, and that because of its personnel it is unique and works with far more "motive" than any other aggregation of public servants in the world. For remember, the vast number of us are those who, having tasted, having felt, and having gained a personal and individual victory, have now enlisted in the most disinterested service. There are few of us who are in this fight for gain; still fewer for fame. But most of us work on because we have been taught by a great disciplinarian and because we would render back some of our mortal hours to the cause that gave them to us. And lest you think that I have now struck the level of sentimentality and that I am indulging more in oratory and in poetry than in fact, let me say that not so many years ago I expostulated with some heat with a man who has stood as high as any in our antituberculosis movement. I tried to point out to him that it was time wasted to spend so much of his precarious strength in public addresses and organized efforts to fight tuberculosis. And he replied that the movement initiated by Dr. Trudeau had given him back his life, that he owed everything he was and had to tuberculosis, and that the least he could do in return was to give up to it every minute he could spare. These were the words of a "lunger." And there are many others like him.

To come back to the disclosures of the Pirquet test. Let us ask how they square with the basic measures of prevention and control as these are embodied in our present program. Let us also seek to discover whether they teach us anything of value that might profitably be employed to supplement our orthodox efforts. But let us first run over briefly the chief weapons of defense that we now employ.

The institutional care of the tuberculous sick has proved its worth and has come to stay. It is yearly rescuing thousands of souls from an early grave or adding to their years. Fundamentally the principles that gave it birth are sound and will withstand any amount of shallow criticism. It has never yet been given a complete test for the simple reason that no community has as yet seen fit to appropriate enough money to take care of every one of its tuberculous patients for a proper length of time. But even though this could be done throughout the entire nation, there is not the shadow of a doubt that institutional care of *itself* would not solve the tuberculosis problem. It would not solve it because infections would still be taking place,—infections that planted the seeds of potential consumption. And infections would continue to take place because it is unthinkable that more than a moiety

of patients would be detected before they had reached the "bacillary" stage, clinically speaking. Therefore, before entering sanatoria a large number will have tuberculized many with whom they live and associate. Properly speaking, institutions for the care of the tuberculous have but small place among the measures of prevention and control. They furnish abodes for reconstruction, education and rehabilitation, and should be looked upon as such. From the point of view of preventive medicine the greatest argument that can be brought forward from them is one of reasoning by analogy,—of comparing them with the lazar-houses that so successfully combated leprosy during the Middle Ages. But the analogy is not quite apt for reasons that would take us too far afield to discuss. We shall here content ourselves with pointing out merely the differences of infectiousness between the two diseases, the differences in onset, and the differences in termination between two diseases, one of which goes on inevitably and in the main progressively to death while the other is eminently a disease of "self-arresting" periods intermingled with relapses, progressions, and retrogressions, that no man can accurately predict, and not too many appreciate.

Even though it could be shown that under certain happy hypothetical conditions which so far as I know have no counterpart on earth, the incarceration of all consumptives would be eminently a preventive measure rather than one of reconstruction, its complete success would be of necessity absolutely dependent upon making a diagnosis in every case of tuberculosis in a stage that precedes the emission of bacilli. This I do not consider even quarter-way possible or practicable. After reading certain discourses on early diagnosis one would get the impression that the ordinary case of tuberculosis originates with the definiteness and abruptness of measles or the semi-obtrusiveness of typhoid fever. But I am confident that there is not a clinician here who will not agree with me that if there is any one feature that only too commonly characterizes the onset of tuberculosis it is that it comes on in such a way that for a considerable time the patient has not the least idea that he is an ill man. He has symptoms, it is true; but what are they? Only too often the same slight disabilities which he has frequently suffered before, and which he more than once shook off. A normal man, unaccustomed to introspection, to hypochondriasis, and to unnecessary self-worry, will not run to a physician because of the slightest indefinite pain or lapse from full efficiency that oppresses him, and it is notorious how often we encounter these symptoms in people in whom we can find no organic basis for their complaints. It is just as notorious how often vague, indefinite and masked symptoms,—deviations from health that do not seriously interfere with a man's pursuit of his occupation—usher in the full expression of tuberculosis. And it is no less notorious how far a tuberculous process may progress anatomically before it addresses itself more eloquently to the patient. All this is so well recognized that I would hesitate to hazard even a guess as to the mean length of time that elapses between the first manifestation of illness and the seeking of medical advice in the ordinary patient who begins

his tuberculosis career as a case of chronic or indefinite onset. I only know this—that I have seen a prominent pediatrician present himself to the phthisiologist for the first time twelve years after his cough had begun. And he arrived with both lungs “riddled” and sputum loaded with bacilli. I have seen an eminent judge first ask for advice thirty-five years after his disease had given out its first warnings. And he came with cavitation in both lungs and a sputum count that would have caused Gaffky to create a new classification: yet he was a supreme court justice and had lost but few days of a busy lifetime from his labors. I also know of a pathologist who for eight years had the symptoms that we classify under the cardio-gastric type of onset, who at last had râles that came and went, and who finally went on to bilateral disease; yet although under constant observation by the best men he was not declared tuberculous until bacilli appeared in his sputum after nine years. The day of his first manifestation of bacilli must of course forever remain unknown, as must the damage that he did between the first “show” of bacilli and the time of their detection.

These cannot be exceptional instances. And they must make us wonder that, if such things are so, what then is going on among the more uninformed. We can only speculate: and I do not believe that the most florid imagination will over-daub the canvas. But if a large number of patients will not seek medical advice until some time after the first manifestation of symptoms, and if the diagnosis of pulmonary tuberculosis can offer insuperable difficulties to the best physicians—and I do consider that both these provisos are actualities that complicate the tuberculosis situation—then, it is manifest, that even though every medical man in the world possessed a degree of diagnostic skill that is at present unimaginable, there would still be ample opportunity left for a fair saturation of the world and the people who live therein with tubercle bacilli. And this statement of necessity carries with it the corollary that, as a measure of control and prevention, early diagnosis must ever be a limping sister.

No, to be of *itself* an adequate preventive method we should have to imagine that the following grotesque approach were workable, namely, that every man, woman and child submit, not monthly, but weekly or even daily, to physical examination and questioning by a competent clinician,—by one who has “tuberculosis judgment.” I say not monthly but weekly or even daily, because tubercle bacilli that have been turned loose can get to many harbors in the space of a month. I use the term “competent” advisely, for reasons that must be apparent to all of you.

Whenever I think of early diagnosis, I think of it, not as a preventive measure essentially or as one of control, but, like institutional care, a salutary measure. And I am never tired of emphasizing that the more physicians there are or will come after us, who from a proper adjudication of history, symptoms, and signs can arrive at an appreciation of the earliest manifestations of clinical tuberculosis, the more human beings there will be who will be snatched from the ravages of the tubercle bacillus. It will reduce somewhat the chances

of infecting others, but, if we honestly face all angles of the situation, the rôle it can play in limiting infection must be as a drop in the bucket. Nevertheless, because it is a life saver, it must ever remain the keystone of the clinical arch of tuberculosis.

We come now to the matter of infection. And here I must pray that I be not misunderstood.

As nearly as I can determine infection is the shibboleth of the antituberculosis campaign. Now and then I go to a tuberculosis exhibit. And what do I see? I see posters everywhere, portraying what we must avoid in this everyday life of ours if we are not to gather to ourselves the tubercle bacillus. I see very visible sneezes and coughs projected toward innocent bystanders. I see clouds of dust cast up by the sweeping broom to the nostrils of anyone who happens to be in the way. I see Susie using Johnny's tooth-brush. I see a pale, though heartless, mother imprint the kiss of instinct upon her baby's lips. All this and much more. And the implication is always plain. This dust, this mouth spray, this vicarious tooth-brush, this kiss, is the cause of consumption.

But is it?

I shall answer by saying that I don't believe it is. It may propel into us the tubercle bacillus. It may even start the anatomical reaction of tubercle. But the number of times that it goes straight on to consumption is negligible,—so negligible that I don't think that we need concern ourselves about it.

Why should we concern ourselves about the *mere presence* of tubercle bacilli in our bodies? The Pirquet test has taught us that all who have taken their place in normal social intercourse have it attached to them. Yet the workers of the world go on, creating and undoing, and amassing and dissipating, all infected, yet few invalidated. Considered by itself, therefore, mere infection is hardly worth paying attention to. It is the normal lot of man. The pessimist, upon first hearing of the universality of tuberculous infection, will throw up his hands and exclaim, “What's the use.” The optimist will throw up his hat, and declare, “It can't be so bad after all. Everyone has it, yet few are sick.”

We should take a far firmer hold on this fact than we have done heretofore. We should spread it broadcast. We should drive it home to every man that before adolescence tubercle is more common than hair on the face, and after forty, more common than hair on the head; and in a great proportion of instances not so troublesome, unless he makes it so. In 1900 it was infection that we were interested in; and naturally so, for it then meant disease. But to-day it is again consumption and its prevention that are our province, for we have learned of how little moment mere infection really is.

I have thus far not dwelt upon one phase of the antituberculous movement that organized effort has always made more than one-half of its program, and which must ever remain its chief function. This is education, so called.

But what is education? Whom shall we educate? And what information shall we impart?

In propagandism we speak much of education. Only too often we seem to imagine that its beginning and end are the dissemination of information. Yet real education is vastly more than this. To scatter broadcast and aimlessly what he knows is wasted time for any teacher. The process of education presupposes that, besides being given, our information is received, understood and assimilated. Only too often we teachers cast our pearls before swine. Only too often, too, we consider our function fulfilled when we have thus delivered ourselves of a weighty homily. And much of the education of health associations has, to my way of thinking, often proceeded in this haphazard fashion. Therefore, when I am told that to-day the people and the medical profession are already "educated" as regards tuberculosis, I react with a gesture of scepticism and unbelief. That tons of literature have been scattered to the four corners I do not doubt. But that pounds of what is really worth while have sunk in I do doubt.

The remedy? Why, teachers: teachers who can make their point, who can inspire and who can direct. If it be desirable to instruct youth to take its place in the world and make its living, how much more important is it that it be taught how to preserve its life! Under the patronage of the state a highly organized body of unselfish men and women are preparing our sons and daughters for the duties of life. And had I my way I would see to it that we of the National Association would select a great corps of the most elect of mankind, of teachers, and send these out to tell their fellow-men how they may preserve their lives. I should attempt to have these teachers trained in all the essential particularities of tuberculosis and of public health. I should send them to the people and I should send them to the physicians. And what would I have these told?

Much more than I can here take up to-night. But I would have emphasized that tuberculosis, a gaunt, manifest, upheaval of pulmonary infection, has its birth, not so much, if you please, in an ert-while localization of the tubercle bacillus, but in any and every event that makes man unhealthy. I would have them told that to be spat upon or coughed upon by the man with the "common cold" did not upset me because I might merely acquire a cold quite so much as that this cold might fan my quiescent pulmonary tubercle into phthisis. I would have them told that the delicate woman who was about to fulfill her grandest function should be handled just a little differently from the sturdy one,—that her labor should be shortened, that her lactation be directed with the possibility of manifest tuberculosis ever kept in mind. I would have them told that over-strain, whether physical or mental, or that dissipation was to be avoided, *not because it lay them open to infection, but because it supplied the oil to a wick that was already present. I would have the emphasis laid on the behavior of the human being and not on the bacillus.* And I should thereby be contributing not only to a solution of the tuberculosis problem, according to the best information available, but also to that larger problem, that of public health in general.

After all, there are only two conceivable short cuts to the eradication of tuberculosis.

The first is the universal use of a remedial agent that would cure any and every type of disease without harm to the patient. We would presume that such a preparation would be bacillicidal. If it was capable of curing every case of manifest disease and could at the same time sterilize all tissues we would presuppose further that it could free from bacilli all foci that lay concealed in those without manifest disease. If, therefore, we were in possession of such a potent medicine, we could at any given time, by edict or by common agreement, administer it to all people and to all animals that are susceptible to the tubercle bacillus and at one grand stroke wipe out all tubercle bacilli that were in parasitic association with tissues. And this would undoubtedly mean the end of tuberculosis on earth.

The second short cut would be to administer to every non-tuberculous individual and to every new-born susceptible animal over a period of several generations a something that would immunize them in a way that they would be secure from any tubercle bacilli that attempted to gain lodgement in their bodies. This, manifestly, would be a more leisurely method than the first; for with only this weapon in our armamentarium, before the bacillus disappeared, we should be obliged to wait until the present myriads of victims,—our phthisical grandfathers and our tuberculous children as well,—squared accounts with their unwilling and ungrateful guests,—obligations of a kind that are never adjusted with finality till Death the only non-appellate arbiter comes between. The more halting of the two, this procedure would, none the less, also spell the end of tuberculosis.

Neither of these short cuts is in sight, nor can our generation hope to take the journey. Meanwhile I would stress that the prevention of tuberculosis is a prevention, not of infection, but of manifest disease; and that all our efforts should be directed to a supplementary reëducation of physician and layman alike, and the study of every factor that makes infection disease. And at the risk of unnecessary repetition I would also point out anew that there is no one shining beacon to lead us to the control and prevention of tuberculosis. The very complexity of the situation forbids this. I would not abate one jot or tittle of any tested method that we have employed. But I would take advantage of what the last decade has brought to us and lay the onus on the human individual rather than on the infecting microorganism.

The opportunity for service in antituberculosis work is tremendous. As the first time casts his eye over the fields to be made over and the roads to be travelled. The opportunities for philanthropy are no less great and in no human endeavor will money spent yield more certain and richer returns. We must have a goal and this goal must be the complete taking-over of the tuberculosis situation throughout the world. We must cry for money and money and still more money, and never cease until the mass of mankind realizes the situation and is responding to it. Then and then only can we say that we are

in a position to wage a real battle against tuberculosis. An effective fight would presuppose an organization the spirit and model of which could be found only in the monastic orders of medieval times. Our sisterhood, made of up thousands who have given back their lives to tuberculosis, would live among the sick and bring them back to a measure of effectiveness. Our friars would go up and down the land instilling the people with the truth,—the truth of the universality of the tubercle bacillus, the truth of the magnitude of its mortal effect, the truth of the inciters of the tubercle bacillus to action, the truth that everything that makes for the internment of the tubercle bacillus within ourselves makes for better living and higher efficiency and that everything that makes for better living and higher efficiency makes for the internment of the tubercle bacillus. Without rest, without interruption or let-up, we must keep all this before the people, while our priors and our abbots are busy in recording the peculiar habits and characteristics of the enemy and the responses and reactions of the body to it. Acquisition of all

information, broadening, intensification, growth, and development, must never cease in our plans of campaign. Apologetic we need not be and dare not be; and no real worker should be obliged to approach the shrine of wealth with hat in hand to ask for a pittance for the cause. It is the glory of mankind that it has always been responsive to necessity; and real information that brings about an adequate appreciation of the necessities of the situation will always loose the purse-strings.

Nor is there room in the antituberculosis movement for a single note of discouragement. The pessimists among us can be only those who are deficient in grasp and breadth. Civilization and tuberculosis are cotemporaneous; the number of the tuberculous and the number of civilized beings are almost coequal; therefore, to despair of tuberculosis is to despair of civilization. A graft that is as much a part of us as is the development of our ethical sense cannot be lopped off in a day; but it can be kept from flowering and bearing fruit. And until we can wage direct warfare on the germ, to keep it in the seed should be our main purpose.

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INSUSCEPTIBILITY OF MONKEYS TO INOCULATION WITH BLOOD FROM MEASLES PATIENTS

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Measles, though usually a mild disease in itself, often leads to serious consequences; its involvement of the upper respiratory tract frequently facilitates the invasion of the lungs by the hæmolytic streptococcus or the pneumococcus. The resulting pneumonia has attracted considerable attention of late. Control of the hæmolytic streptococcal infections by specific vaccines or serum therapy is a difficult problem. A possible departure from this line of approach consists in the prevention of measles itself by the development of a prophylactic inoculation. The clinical features of the disease indicate the existence of an excellent theoretical basis for the development of a protective inoculation. One attack of measles confers a high degree of immunity, and the virulence of the causative organism is naturally so low that *per se* it does not produce fatal effects in man under ordinary conditions. The crucial problem is whether the virus of measles can be still further attenuated in such a manner that it would be suitable for prophylactic purposes.

On the recommendation of Colonel Frederick F. Russell the problem of prophylactic inoculation against measles is being investigated. Unfortunately, the causative organism of the disease is not known. A variety of bacteria have been cultivated from the blood and the mucous exudates of patients, but evidence of the etiologic importance of these organisms has not been produced. It has generally been considered that Hektoen,¹ by inoculations into man, has established the existence of the virus of measles in the circulating blood at least during the first day after the rash appears. Four groups of workers have reported on very slight evidence that monkeys are susceptible to the disease. These meager data constitute the essential features of the experimental work that has been conducted on measles.

Review of Literature.—In attempting the attenuation of the virus of measles, one of the first points obviously consists in determining the susceptibility of lower animals. Important symptoms have been attributed to the inoculation of the blood of measles patients into monkeys. Compiling the effects noted by various workers we have the following:

(1) Fever, (2) rash, (3) Koplik spots, (4) leucopenia, (5) rhinitis and (6) malaise. Of these symptoms Anderson and Goldberger² noted especially the development of fever accompanied frequently by a rash, by coryza, rhinitis and malaise. Very significant or clearly marked results were reported for all monkeys injected with the blood taken from unquestionably early cases of measles, i. e., within from 12 to 24

hours after the appearance of the rash. The very doubtful or negative results are considered as having occurred when the blood was withdrawn during the second day of the rash. Well-marked febrile reactions with an exanthem were obtained not only by the injection of serum, but also with very thoroughly washed red cells. Three species of monkeys were found susceptible to inoculation with blood, namely, *Macacus rhesus*, *M. cynomolgus* and *M. sinicus*.

Nicolle and Conseil³ report the transmission of measles to a monkey (*M. sinicus*). They injected one animal with blood taken from a patient 24 hours before the appearance of the eruption; after an incubation period of nine days, a slight elevation of temperature occurred unaccompanied by any other symptoms.

Hektoen and Eggers⁴ studied the leucopenia and also the temperature reaction in *M. rhesus*. Two of three animals that were inoculated showed a transient rise in temperature; a pronounced drop in the white count was noted on the sixth day in one and on the ninth in the other, the leucopenia persisting somewhat irregularly for several days. Differential counts showed the leucopenia to be due principally to a drop in the polymorphonuclear cells. One animal apparently became ill on the 12th day and on the 15th a maculopapular eruption appeared and persisted for several days. No Koplik spots were seen. The development of a leucopenia in *M. rhesus* after the inoculation of measles blood has been confirmed by Tunncliffe.⁵

Hektoen and Eggers interpret this leucopenia as indicating a reaction to the virus of measles. Their results taken in conjunction with Anderson and Goldberger's work lead them to conclude that monkeys develop a mild kind of measles when injected with blood from patients taken soon after the rash has appeared.

Lucas and Prizer⁶ selected a case of measles in a child and inoculated two monkeys with blood taken six hours before the appearance of the rash. These monkeys developed a transient erythema of the face, a leucopenia and Koplik spots. These spots appeared on the 10th day after inoculation, but unfortunately the period of their duration was not recorded. It is not stated whether isolated spots were found or whether typical clusters occurred. No febrile reactions were obtained and the temperature of these animals was not reported. Unfortunately, these animals died about two weeks after inoculation from an intercurrent infection of unknown etiology. Several uninoculated control monkeys also died.

It is evident, then, that these studies are not very conclusive; the blood counts under these circumstances are particularly unreliable. Lucas and Prizer conclude that these monkeys were undoubtedly infected with measles.

Anderson and Goldberger, Hektoen and Eggers, Lucas and Prizer, report the successful passage of the virus of measles from monkey to monkey by the inoculation of blood. Anderson and Goldberger report six successive passages without any change in virulence. Nicolle and Conseil attempted on one occasion to subinoculate from one monkey to another, but without success.

Outline of Work.—In the following experiments, monkeys (*M. rhesus*) were inoculated from cases of measles occurring in adults 20 to 30 years of age. Blood was the only material used for inoculation, and in all cases it was withdrawn within the first 24 hours after the appearance of the rash. It was either defibrinated or collected in sodium citrate solution prepared in physiological saline. In some instances it was diluted with several parts of salt solution, according to the recommendations of Ricketts and Wilder⁷ for the transmission of typhus to monkeys and also according to Hektoen and Eggers' work on measles. Observations on the inoculated animals were made each day about the middle of the forenoon, especial attention being given to the body temperature and the leucocyte count. The room temperature was also recorded, because, under normal conditions, the temperature of monkeys fluctuates somewhat. The buccal mucous membranes were examined from time to time for the appearance of Koplik spots. Excellent housing conditions were available for the animals, thereby avoiding any difficulty from the spontaneous development of rhinitis or coryza during the incubation period.

In order to test out any doubtful symptoms occurring in the inoculated monkeys, arrangements were made to inject blood from them into a susceptible human volunteer. In the selection of a human subject two points were given especial consideration, namely (1) assurance that the individual had never had a recognizable attack of measles, and (2) rejection of any individuals harboring pathogenic organisms in the respiratory passages.

It was found that very little dependence could be placed on the statement of even the educated adult that he had never had measles. Those men who could not remember an attack of the disease were asked to confer with their family; only those were accepted in whom there was no suspicion of an attack of either measles or rubella.

In addition to the routine physical examination, special care was taken to insure that the tonsils and sinuses were in good condition. In the case of enlarged tonsils, the hæmolytic streptococcus may occur in the crypts even when the surface of the gland is free from pathogenic bacteria.

Bacteriological examinations were made primarily for the hæmolytic streptococcus and pneumococcus. Examinations were also made for the meningococcus, the diphtheria and the influenza bacillus. Cultures were made over a period of from two to three weeks at intervals of from five to seven days, so

that each individual was examined at least three times. As regards tuberculosis, attention was given to the history, the physical examination and the X-ray findings in the chest.

In considering the inoculation of a human subject precautions were taken against micro-organisms that might secondarily invade the blood stream of measles patients. It was necessary to avoid the possibility of carrying any such micro-organisms from the measles patients over to the monkeys and back again to a human subject. In making blood cultures in cases of measles, Tunnick⁸ found a very considerable variety of bacteria. These secondary invaders appeared in the blood stream to an extent even greater than that occurring in scarlet fever. Therefore, we have made cultures on all specimens of blood inoculated into the monkeys.

Cultures were made aëroically in flasks of hydrocele meat infusion broth without sugar and also anaëroically according to the technique used by Plotz⁹ in his work on typhus fever. For the anaërobic cultures, a few cubic centimeters of hydrocele fluid in ordinary test-tubes were inoculated with varying amounts of blood and the tubes filled with 2 per cent glucose meat infusion agar of a reaction to phenolphthalein corresponding to from 0.2 to 0.5 per cent of normal acid. Cultures were not discarded till after one month's incubation. Except for two contaminating colonies, no growth was obtained in seven cases cultured during the first day after the rash appeared. One of these patients was recultured during the second day of the rash with negative results. With a similar technique, Plotz also failed to obtain any growth from the blood of measles patients, studied as controls for his work on typhus fever.*

Results of the Inoculation of Monkeys.—Two adult monkeys were inoculated intraperitoneally, each from a different case of measles. Neither of these animals developed any symptoms that were diagnostic of the disease or that furnished any guide as to the most appropriate time for reinjection into a susceptible subject. It has been found that monkeys which fail to react to an injection of typhus blood may frequently respond to a subsequent injection; these two animals were therefore reinjected intraperitoneally with measles blood. At the same time a third normal monkey was also injected. In order to increase the opportunity for infection, these animals were injected every day for three successive days, each injection being made from fresh cases of measles.

On the first day, the normal monkey was injected into the heart and into the peritoneal cavity; all other injections of this and the other two animals were made intraperitoneally. Intracerebral inoculations were not used on account of the possible interference with the temperature reactions. There is no logical foundation for them in measles, and according to Anderson and Goldberger's results this method apparently possesses no superiority over intraperitoneal injection.

These monkeys were observed for a period of three and a half weeks after their last inoculation. No symptoms developed which differed in any essential way from changes

* Personal communication.

that were noted during control periods of observation. The temperature curves remained entirely normal. The white counts fluctuated considerably and occasionally would drop for a single day, but there was no leucopenia that was sustained even for a short period. The temperature of Monkey I was somewhat elevated on the 15th and 16th days after the second series of inoculation, but the leucocyte count rose also at this time. In no case did we obtain the combination of a high temperature accompanied by a leucopenia. Another monkey (II) developed a pronounced erythema with a few macules 10 days after inoculation, but this was hardly as marked as a similar rash which appeared in this animal one week before injection. It was not preceded nor accompanied by Koplik spots. The continued absence of lesions in the rather delicate mucous membrane would seem to militate against interpreting the skin eruption as due to measles. This same criticism applies to the rash without Koplik spots observed by Hektoen and Eggers.

Neither of the other two monkeys developed any lesions in the skin or mucous membranes. All three remained entirely free from conjunctivitis, rhinitis and coryza. There was no loss of appetite and no evidence of malaise.

Notwithstanding the negative results in these animals it is theoretically possible that the virus may have persisted and even multiplied without producing symptoms. Accordingly, the monkey (III) which had not previously been injected with measles was bled on the 11th day after the first of the three successive injections; after defibrination 3.5 c. c. of this blood was injected at once subcutaneously into a human volunteer. No symptoms developed. Anaërobic cultures of this blood showed no growth. Although this subject apparently never had measles, it is possible that he may have had an attack so mild as to be unrecognized yet sufficient to produce immunity. In order to obtain final proof that this specimen of blood did not contain the virus of measles it would be necessary to establish the susceptibility of this individual to measles. It is not justifiable to obtain such proof experimentally in view of the entirely negative results obtained in the monkeys.

On the basis of Hektoen's striking results it was assumed that the subcutaneous injection of a small amount of blood containing the virus of measles would reproduce the disease in man. In another series of investigations on prophylactic inoculation, a very unexpected result was obtained. One-half c. c. of serum from a fresh case of measles was inoculated subcutaneously without delay into an apparently susceptible individual; this quantity is several times larger than that used by Hektoen. This subject remained entirely free from any symptoms of the disease. This result in man casts a little additional doubt on the transmission of measles to monkeys by the inoculation of blood.

Discussion.—In the investigation of the circulating blood for the virus of measles, it would seem that trustworthy progress cannot be made by the inoculation of monkeys. Even though slight symptoms do develop in occasional in-

dividual animals it would appear that the results are too inconstant and indefinite to permit the practical use of this animal. Some more accurate means for the diagnosis of measles must be obtained before it can be clearly established that the monkey is, at times, infected by the injection of blood from early cases. It is conceivable that infection of this species with measles might be obtained in some other manner; for example, by scarifying the mucous membranes with the virus using perhaps the secretions from the respiratory tract instead of the blood of patients.

Anderson and Goldberger report that the injection into monkeys not only of blood serum, but also of very thoroughly washed corpuscles produced a well-marked reaction with an exanthem. This result suggests that the virus of measles occurs in the red cells as well as in the serum, since in the typical bacteremias the organisms adhering to washed corpuscles would hardly be sufficient to infect a distinctly refractory animal. However, there is good evidence that all of the diseases known to be caused by typical protozoan parasites of the red cells are transmitted by insects, whereas dropped infection constitutes the usual mode of propagation in measles. This apparently equal distribution of the virus of measles between the red cells and the serum is difficult to explain.

SUMMARY

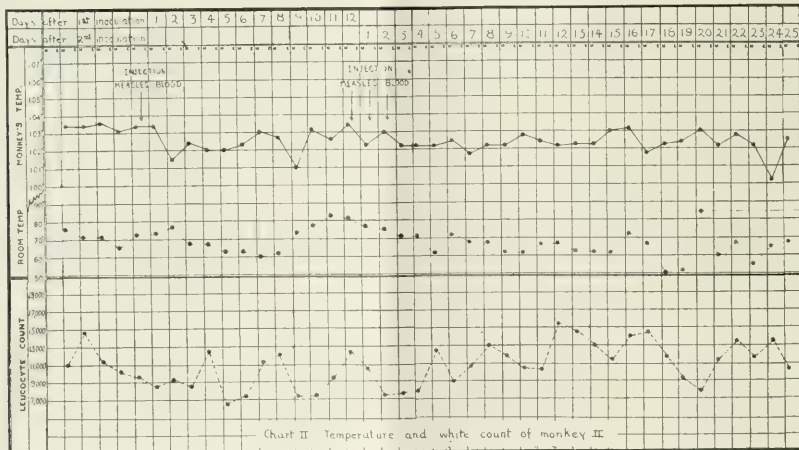
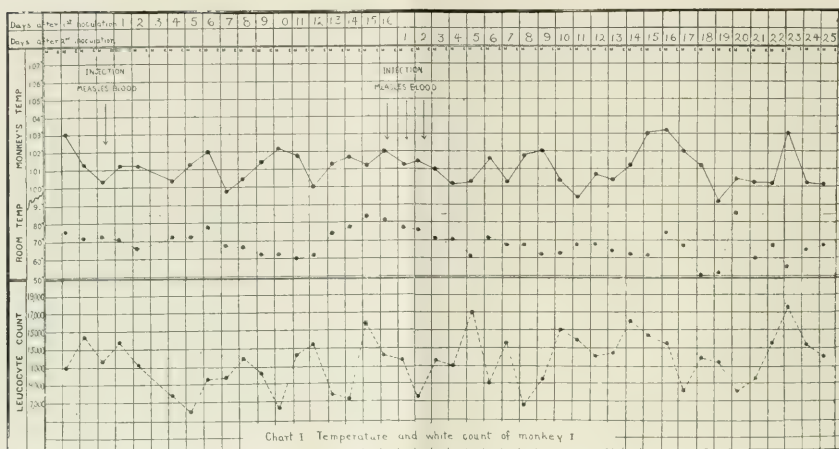
1. Three monkeys were inoculated with the blood of measles patients taken early in the course of the disease from moderately severe cases. These animals remained entirely free from any symptoms that were either diagnostic or even suggestive of measles. Two of these animals that were injected a second time failed to develop any symptoms.

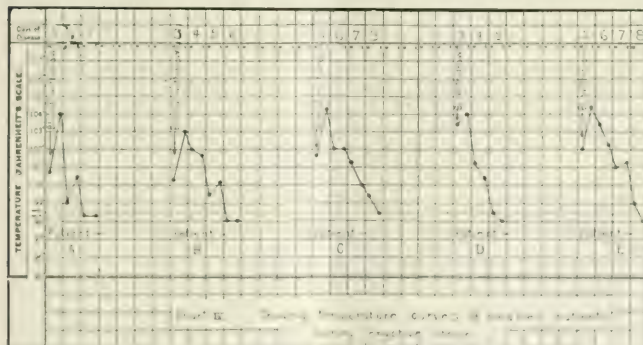
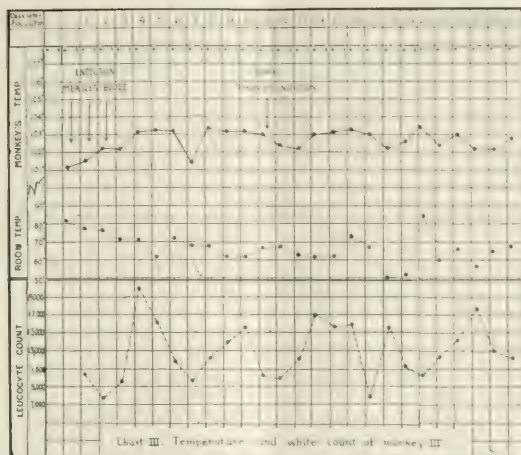
2. After an incubation period of 11 days blood was taken from one of these monkeys and injected into a human volunteer. No symptoms developed.

PROTOCOLS

The following data give the details concerning the injection of these monkeys; the record of their temperatures and white counts is given in full in order to provide the data on which we have based the interpretations given in the text. The temperature charts of the measles patients are given in order to show the stage of the febrile period at which the blood was withdrawn. This information as well as the statements concerning the time of appearance of the rash furnishes an indication of the period of the disease at which the subinoculations were made.

Monkey I was kept under observation for one week. Ten cubic centimeters of blood were taken from a case of measles (Patient A) 18 hours after the first appearance of the rash. This blood was diluted with 40 c. c. of physiological saline, then defibrinated and injected intraperitoneally. Chart I shows the temperature and white blood count of this animal. The temperature chart of the patient (Chart IV) shows that the blood was taken before the infection had begun to decline.





Sixteen days after this injection, this animal was reinoculated with measles blood taken from a patient (C) within from four to six hours after the rash had appeared. The blood was mixed with an equal part of 2 per cent sodium citrate in physiological saline. Of this mixture 15 c. c. were injected intraperitoneally. On the following day, 24 hours later, another injection was made with blood taken from a patient (D) 12 hours after the appearance of the rash. This specimen of blood was diluted with an equal part of physiological saline and defibrinated; 20 c. c. of this defibrinated mixture were injected intraperitoneally. After another interval of 24 hours a final injection was made with the blood of Patient E, taken not later than 12 hours after the rash had appeared. One part of blood was mixed with two parts of physiological saline and 20 c. c. of the defibrinated mixture were injected intraperitoneally. The effect of these injections is given in Chart I. The temperature charts of these patients are also given. (Chart IV.)

Monkey II was kept under observation for 10 days. Blood for injection was taken from Patient B within from 6 to 12 hours after the first appearance of the rash. The specimen was mixed with an equal part of physiological saline and 20 c. c. of the defibrinated mixture were injected intraperitoneally. The white blood counts and temperature of this animal are given in Chart II. The temperature of the patient is recorded in Chart IV. Before injection this animal had a marked erythema over the face and eyebrows; a few macules were also present. This rash faded during the first week of the incubation period, but increased somewhat 10 days after inoculation, though its intensity was not so great as during

the period before injection. Since this time it has fluctuated considerably. At present, two months after the last injection, it is more marked than at any time during the incubation periods. Twelve days after the first injection of blood this monkey received injections of measles blood on three successive days; these injections were exact duplicates of those just recorded for Monkey I, the same specimens of blood being used.

Monkey III. This animal, a young adult, was given a series of three injections simultaneously with Monkeys I and II. The same specimens of blood were employed though the details were different. The injection on the first day consisted of 8 c. c. of the mixture of citrated blood injected into the heart and 12 c. c. intraperitoneally. On the second and third days 30 c. c. of the defibrinated mixtures were given intraperitoneally. The results in this monkey are recorded in Chart III.

REFERENCES

1. Hektoen: Jour. Infect. Dis., 1905, II, 238.
2. Anderson and Goldberger: Public Health Reports, 1911, XXVI, 847 and 887; Jour. Am. Med. Assn., 1911, LVII, 113, 476 and 971.
3. Nicolle and Conseil: Compt. Rend. Acad. Scien., 1911, CLIII, 1522.
4. Hektoen and Eggers: Jour. Am. Med. Assn., 1911, LVII, 1833.
5. Tunncliffe: Jour. Infect. Dis., 1912, XI, 474.
6. Lucas and Prizer: Jour. Med. Research, 1912, XXVI, 181.
7. Ricketts and Wilder: Jour. Am. Med. Assn., 1910, LVI, 463.
8. Tunncliffe: Jour. Infect. Dis., 1918, XXII, 462.
9. Plotz: Jour. Infect. Dis., 1915, XVII, 1.

THE PRODUCTION OF TETANY BY THE INTRAVENOUS INFUSION OF SODIUM BICARBONATE

REPORT OF AN ADULT CASE

By GEORGE A. HARROP, JR.

(From the Medical Clinic of The Johns Hopkins Hospital)

Many drugs and chemicals have been mentioned as causing tetany in adults. Following Frankl-Hochwart,¹ it has been customary to classify all these conditions in one group, as due to toxins or poisons. The clinical history of a patient with tetany which was produced, or at least precipitated, by intravenous infusions of sodium bicarbonate follows:

L. H. Medical No. 39293. Colored. Aged 22. Domestic. Admitted, March 8, 1918. Died, March 18, 1918.

The family and past history were unimportant, except that the patient remembered no previous attacks which in any way suggested tetany, and the members of her family corroborated her statement.

Present Illness.—At 7.30 a. m. on the day of admission, before she had taken any food, she swallowed two 7½-grain tablets of bichloride of mercury, dissolved in a glass of water. Shortly afterward she vomited, and within an hour commenced to vomit

blood. She was admitted to the hospital about noon. At this time she was vomiting dark colored material, and was very dull and drowsy.

Physical Examination.—Nothing abnormal was made out aside from tenderness and slight muscle spasm in the upper abdomen. The throat was red, but otherwise it showed nothing. All of the deep reflexes were normally active. No stigmata of rachitis could be found. Weight, 130 pounds. Mercury was recovered from the urine, feces, and vomitus.

Blood Examination.—W. B. C., 19,000. R. B. C., 5,624,000. Hemoglobin (Sahli), 90 per cent. Differential blood count normal. The Wassermann test was negative.

Course in the Hospital.—From the time of her admission the patient passed blood in her urine and stools. The usual energetic measures were taken to secure a large fluid intake and to eliminate the mercury.

On March 9 she became totally anuric and continued so until her death. On this day the plasma bicarbonate capacity (Van Slyke) was 45 volumes per cent, and the carbon dioxide tension of the alveolar air (Marriott) was 28 mm. of mercury. She was

¹ Frankl-Hochwart: Die Tetanie der Erwachsenen, Leipzig, 1907.

given 500 c.c. of a 5 per cent sodium bicarbonate solution intravenously.³ No untoward effect was noted and she said that she felt more comfortable afterwards.

Twenty-four hours later (March 10), another intravenous infusion was given of 700 c.c. of a 5 per cent sodium bicarbonate solution, prepared as before. This made in all 60 grams of sodium bicarbonate given intravenously. A small amount given by mouth on March 9 had not been retained. About five minutes after this last infusion, which had been given slowly and had been apparently well taken, the patient's face suddenly grew pale, she commenced to have great inspiratory difficulty, and became very apprehensive. She complained of numbness and tingling of the fingers, and begged to have them rubbed. The hands assumed the typical obstetrical position, there was pedal spasm, and a first degree facial phenomenon (Chvostek's sign) was obtained. The pulse was accelerated to about 130, and the extremities became cold. There was no elevation of the blood-pressure. The acute attack lasted for about 15 minutes, after which the breathing became easier and she was less apprehensive. The *main d'accoucheur* position was maintained for about two hours.

On March 11 a blood sample was taken for the calcium and phosphate determinations recorded below, and at the same time for a determination of the plasma bicarbonate capacity (Van Slyke), which was found to be 80 volumes per cent. This sample was taken about 20 hours after the original attack. On this day a second degree Chvostek's sign was obtained and Trousseau's phenomenon was easily elicited.

The further history of the case has no bearing on the present discussion, except that Trousseau's phenomenon was present until March 15, and Chvostek's sign was obtained the night before her death, March 18. Commencing on March 12 there was pitting edema of the lower legs, and on March 15 evidence of the accumulation of a moderate ascites. She became very anemic from the continued bleeding from the bowel, the hemoglobin (Sahli) on March 17 being only 20 per cent.

³ This was prepared by boiling a sodium bicarbonate solution made up with freshly distilled water, and then reconverting the carbonate so formed back into the bicarbonate by passing a stream of carbon dioxide through the solution until it was no longer colored by a few drops of phenolphthalein.

The writer has been unable to find any clinical reports of tetany occurring in adults following the administration of sodium bicarbonate. Among the many accidents following its use in the treatment of diabetic coma, the occurrence of convulsions, especially clonic in type, is frequently mentioned.⁴ These convulsions have usually led to a rapid fatal termination, often in a few hours. Tetany, however, has not been mentioned or identified as such. Howland and Marriott have observed tetany in young children following the therapeutic administration of sodium bicarbonate for acidosis and cite three cases.⁵ During the period of tetany their patients showed a low calcium content of the blood serum, a condition which they have shown to be present during the active period of infantile tetany, particularly during or shortly after the occurrence of convulsions. The amount is usually then less than 7.0 mg. per 100 c. c. In the present case of adult tetany, analysis of the calcium content of a blood serum sample taken 20 hours after the original attack showed a value higher than 9.0 mg. per 100 c. c., hence about normal, and there was no marked accumulation of phosphates (the phosphate content of the blood serum was less than 6.0 mg. per 100 c. c.).⁶ It should be noted, however, that in this case there had been no actual convulsions. It seems clear that the condition here was associated with, if not directly precipitated by, the suddenly increased alkalinity of the blood due to the sodium bicarbonate infusions.

In conclusion, it is desired to call attention to a danger, not too remote, attendant upon the intravenous use of sodium bicarbonate in conditions in which the renal excretory function is markedly impaired, and particularly when extreme oliguria or anuria is present.

⁴ L. Blum: *Ergeb. der inn. Med. u. Kinderh.* 1913, XI, 480. "Symptomatologie und Therapie des Coma diabeticum."

⁵ *Quart. Jour. Med.*, 1918, XL, 289.

⁶ The calcium and phosphate determinations were kindly made by Dr. Howland and Dr. Marriott.

CHANGES IN THE BLOOD IMMEDIATELY FOLLOWING TRANSFUSION

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The ever-increasing use of transfusion as a therapeutic measure has stimulated interest to seek a clear explanation for the various changes that follow the introduction into one individual of the blood of another. Nevertheless, some of the simplest questions raised by this procedure remain still unanswered. For instance, although it is generally known that after a transfusion the hemoglobin and the red corpuscle values are increased, the exact way in which the increase occurs is not understood. Many have assumed that the immediate effect is entirely mechanical, that is, that the blood of the recipient is altered in direct proportion to the quantity of the blood introduced, just as though the two had been mixed in a vessel outside of the body; that, later, reactions on the

part of the blood-forming organs come into play, and these then take a part in determining the succeeding changes. No doubt the mechanical and reactive effects are both important, but the relative importance of each is not clearly defined, and the decision has practical value, because the outcome may influence us to use either small transfusions frequently repeated or larger transfusions at longer intervals.

Certain observations already at hand cast considerable doubt upon the view that the immediate effects of transfusion are purely mechanical and lead us at once to anticipate that these effects will be neither constant nor quantitative. Lamsen¹ has shown how quickly and markedly the number of red cells in the circulation may be altered by the injection

of adrenalin. He is convinced by his experiments that the liver acts as a reservoir from which large numbers of red cells are poured into the circulation. No doubt other influences may act in the same prompt way upon this reservoir. Sellards and Baetjer,² from their experiments and a review of the entire subject, conclude that there is no constant nor quantitative response to the injection of foreign abnormal elements into the blood. The object of the present study is to obtain detailed and exact information upon the changes that occur in the blood elements immediately after transfusion.

METHODS

Transfusion was performed in each instance by a modification of the citrate method of Lewisohn, as described by Sydenstricker, Rivers and Mason.³ The details of the technique need not be repeated here. Especial care was taken in testing the donors to be certain that the bloods were compatible. The amounts of blood given in different cases varied from 250 c. c. to 1250 c. c. Studies of the blood were made immediately before the injection, immediately after the injection, two hours, five hours and about twenty-four hours later. These time intervals were followed rather closely in practically all of the cases. Each examination consisted of counts of the red cells and of the white cells, with a differential count of 300 white cells. Platelets were estimated in the smears and the hemoglobin was determined. Notes were also made on the morphology of the blood cells. Counts were always made with the same instruments and by the same observer, with the same reagents; and care was taken to draw the blood from the same part of the body, with uniform punctures.

The effect of transfusion was studied in seven cases of pernicious anemia, two cases of idiopathic purpura, four of benzol poisoning, five of secondary anemia and two of Banti's disease.

RESULTS

Responses to transfusion were so variable that it seems desirable to append the detailed protocols. A few of the main points only will be summarized here.

Red Blood Cells.—In general, following the injection of blood, there was an immediate increase in the red cell count, the striking point being the marked increase in many cases apparently out of proportion to the quantity of blood introduced. Thus, in Case 2, the red count rose from 880,000 to 1,488,000 immediately after the injection of 500 c. c.; and in Case 5, from 480,000 to 1,300,000, following the injection

of 650 c. c. Such remarkable changes indicate apparently a rapid redistribution of blood following an injection. In some cases the initial increase continued for several hours, usually falling, so that at the end of 24 hours the count had fallen to approximately where it was before transfusion. In other cases, however, there was a marked increase at the end of 24 hours. In several instances, after injection of blood, the count fell for a few hours and then rose slightly.

Hemoglobin.—The hemoglobin in most cases showed a uniform rise following transfusion, usually reaching its maximum at the end of 24 hours. In some cases the hemoglobin fell slightly after the initial rise. Changes in hemoglobin did not run parallel with changes in the red count, as may be seen best from the variations in the color indexes.

Leucocytes.—In practically every case following transfusion there was some increase in leucocytes. In several instances, however, they remained practically stationary or even fell. These relations do not seem to be constant in any particular type of case. The most striking change in the differential count is the increase in the polymorphonuclear neutrophils, which was striking even in some cases where there was little change in the total leucocyte count. Occasionally a neutrophilic myelocyte was seen following transfusion, but they were not constant. In these cases no outpouring of nucleated red cells occurred, although in four instances a few were seen following transfusion, but not before. The numbers are so small, however, that this may have been accidental.

DISCUSSION

A general review of the immediate effect of transfusion upon the blood count in twenty cases does not reveal any constant changes following this procedure. The point of practical interest and importance seems to be that no exact mechanical effect can be demonstrated following the introduction of definite quantities of blood. Whereas, in a general way, it may be said that the introduction of blood raises the count, the effect is essentially a biological one involving the redistribution of blood in the body and its exact nature is not at present understood.

REFERENCES

1. Lamson: Jour. Pharmacol. and Exp. Therap., 1915, VII, 169.
2. Sellards and Baetjer: Bull. Johns Hopkins Hosp., 1918, XXIX, 135.
3. Sydenstricker, Mason and Rivers: Jour. A. M. A., 1916, 117, 719.

BLOOD CHART—CASE 1

PATIENT'S NAME, BRANT; WARD F; AGE, 47; MEDICAL NO., 124833; DIAGNOSIS, PERNICIOUS ANEMIA; TRANSFUSION, 1250 C. C.

Date	5-31-18	5-31-18	5-31-18	5-31-18	6-1-18	Remarks
Time	Before Transfusion 4:00 p. m.	After Transfusion 5:30 p. m.	7:00 p. m.	12:00 p. m.	4:00 p. m.	
	I	II	III	IV	V	
P. M. N.	143	47.6%	166	47.6%	180	60.0%
P. M. E.	4	1.33%	5	1.33%	0	0
P. M. B.	0	0	0	0	0	0
L. Lym.	1	0.33%	0	0	0	0
S. Lym.	146	48.0%	114	32.0%	99	33.0%
L. Mono.	7	2.17%	8	2.22%	3	1.00%
Trans.	4	1.33%	5	1.33%	0	0
N. Myelocytes	0	0	0	0	0	0
E. Myelocytes	0	0	0	0	0	0
R. Myelocytes	0	0	0	0	0	0
M. Myelocytes	0	0	0	0	0	0
Smudges	14	4.60%	6	2.00%	45	15.00%
Platelets	Markedly decreased.	Markedly decreased.	Markedly decreased.	Markedly decreased.	Markedly decreased.	
Nucleated R. B. C.	2-Intermediate, 1 Normoblast, 1	Moderate anisocytosis. Moderate poikilocytosis.	Moderate anisocytosis. Moderate poikilocytosis.	Moderate anisocytosis. Moderate poikilocytosis.	Moderate anisocytosis. Moderate poikilocytosis.	
Reticulocytes	Slightly diffused and punctate.	Slightly diffused and punctate.	Slightly diffused and punctate.	Slightly diffused and punctate.	Slightly diffused and punctate.	
No. Cells Counted and %	99.91	99.98	99.96	99.93	99.98	
Hb.	99%	99%	99%	70%	70%	
R. B. C.	2,281,000	3,124,000	3,380,000	2,960,000	2,688,000	
W. B. C.	3,200	4,300	3,340	3,400	4,440	
C. I.	1.3	.95	1.0	1.2	1.3	
Condition of Patient	No chill; no fever.	No chill; no fever.	Slight fever.	Slight fever.	Slight fever.	
Blood Obtained	Little finger left hand.	Third finger left hand.	Little finger left hand.	Third finger left hand.	Little finger left hand.	P. transfused slowly on right arm.

BLOOD CHART—CASE 2

PATIENT'S NAME, PAYUK; WARD G; AGE, 30; MEDICAL NO., 123834; DIAGNOSIS, PERNICIOUS ANEMIA; TRANSFUSION, 500 C. C. 2d TRANSFUSION

Date	3-26-18	3-26-18	3-26-18	3-26-18	3-27-18	Remarks
Time	Before Transfusion 3:55 p. m.	After Transfusion 4:15 p. m.	6:15 p. m.	9:30 p. m.	2:40 p. m.	
	I	II	III	IV	V	
P. M. N.	187	60.3%	199	66.3%	98	89.3%
P. M. E.	9	3.07%	9	3.07%	0	0
P. M. B.	1	0.33%	1	0.33%	0	0
L. Lym.	1	0.33%	16	5.33%	4	1.33%
S. Lym.	68	22.6%	57	19.0%	15	5.0%
L. Mono.	4	1.33%	8	2.66%	10	3.33%
Trans.	7	2.33%	11	3.66%	1	0.33%
N. Myelocytes	0	0	0	0	0	0
E. Myelocytes	0	0	0	0	0	0
R. Myelocytes	0	0	0	0	0	0
M. Myelocytes	0	0	0	0	0	0
Smudges	7	2.33%	2	0.66%	2	0.66%
Platelets	Practically absent.	Moderately diminished.	Markedly diminished.	Moderately diminished.	Moderately diminished.	
Nucleated R. B. C.	1-Normoblast, 1 Marked anisocytosis. Marked poikilocytosis.	1-Normoblast, 1 Marked anisocytosis. Moderate poikilocytosis.	1-Normoblast, 1 Slight anisocytosis. Moderate poikilocytosis.	1-Normoblast, 3 Marked anisocytosis. Moderate poikilocytosis.	0 Moderate anisocytosis. Moderate poikilocytosis.	
Reticulocytes	Slightly diffused.	Slightly diffused and punctate.	Slightly diffused.	Slightly diffused.	Slightly diffused.	
No. Cells Counted and %	99.94	99.94	99.95	99.99	99.99	
Hb.	99%	99%	99%	99%	99%	
R. B. C.	1,488,000	1,488,000	1,512,000	1,472,000	1,400,000	
W. B. C.	4,300	4,300	3,700	3,700	3,700	
C. I.	1.1	1.0	1.0	1.0	1.0	
Condition of Patient	No chill; no fever.	No chill; no fever.	Slight fever.	Fever.	No chill; no fever.	
Blood Obtained	Little finger right hand.	Third finger right hand.	Little finger right hand.	Third finger right hand.	Little finger right hand.	P. transfused slowly on right arm.

BLOOD CHART—CASE 3

PATIENT'S NAME, PAYUK; WARD G; AGE, 30; MEDICAL NO., 123834; DIAGNOSIS, PERNICIOUS ANEMIA; TRANSFUSION, 500 C. C.

Date	3-12-18	3-12-18	3-12-18	3-12-18	3-13-18	Remarks
Time	Before Transfusion 11:00 a. m.	After Transfusion 12:25 p. m.	2:25 p. m.	5:25 p. m.	11:00 a. m.	
	I	II	III	IV	V	
P. M. N.	187	60.3%	199	66.3%	98	89.3%
P. M. E.	9	3.07%	9	3.07%	0	0
P. M. B.	1	0.33%	1	0.33%	0	0
L. Lym.	1	0.33%	16	5.33%	4	1.33%
S. Lym.	68	22.6%	57	19.0%	15	5.0%
L. Mono.	4	1.33%	8	2.66%	10	3.33%
Trans.	7	2.33%	11	3.66%	1	0.33%
N. Myelocytes	0	0	0	0	0	0
E. Myelocytes	0	0	0	0	0	0
R. Myelocytes	0	0	0	0	0	0
M. Myelocytes	0	0	0	0	0	0
Smudges	7	2.33%	2	0.66%	2	0.66%
Platelets	Practically absent.	Moderately diminished.	Markedly diminished.	Moderately diminished.	Moderately diminished.	
Nucleated R. B. C.	6-Normoblast, 4 Intermediate, 1 Marked anisocytosis. Marked poikilocytosis.	1-Normoblast, 1 Marked anisocytosis. Moderate poikilocytosis.	1-Normoblast, 1 Slight anisocytosis. Moderate poikilocytosis.	1-Normoblast, 3 Marked anisocytosis. Moderate poikilocytosis.	0 Moderate anisocytosis. Moderate poikilocytosis.	
Reticulocytes	Slightly diffused.	Slightly diffused and punctate.	Slightly diffused.	Slightly diffused.	Slightly diffused.	
No. Cells Counted and %	99.94	99.94	99.95	99.99	99.99	
Hb.	99%	99%	99%	99%	99%	
R. B. C.	1,488,000	1,488,000	1,512,000	1,472,000	1,400,000	
W. B. C.	4,300	4,300	3,700	3,700	3,700	
C. I.	1.1	1.0	1.0	1.0	1.0	
Condition of Patient	No chill; no fever.	No chill; no fever.	Slight fever.	Fever.	No chill; no fever.	
Blood Obtained	Little finger left hand.	Third finger left hand.	Little finger left hand.	Third finger left hand.	Little finger left hand.	P. transfused slowly on right arm.

BLOOD CHART—CASE 4

PATIENT'S NAME, ALEXANDER; WARD F; AGE, 33; MEDICAL NO. 125655; DIAGNOSIS, PERNICIOUS ANEMIA; TRANSFUSION, 750 C. C.;

2D TRANSFUSION

Date	6-29-18 Before Transfusion 11.00 a. m.	6-29-18 After Transfusion 12.25 p. m.	6-29-18 2.25 p. m.	6-29-18 5.25 p. m.	6-30-18 11.00 a. m.	Remarks					
	I	II	III	IV	V						
P. M. N.	146	48.6%	148	49.3%	219	73.0%	177	59.1%	262	67.3%	A few pathol. lymphocytes seen in I, II, III.
P. M. E.	11	3.6%	12	4.0%	8	2.6%	14	4.6%	5	1.6%	
P. M. B.	0	0	0	0	1	0.33%	0	0.33%	2	0.66%	
L. Lym.	4	1.33%	1	0.33%	0	0	0	0	1	0.33%	
S. Lym.	123	41.0%	129	43.0%	62	20.6%	95	31.6%	57	19.0%	
L. Mono.	6	2.0%	3	1.0%	3	1.0%	4	1.33%	12	4.0%	
Transitional	7	2.33%	5	1.66%	2	0.66%	5	1.66%	7	2.33%	
N. Myelocytes	0	0	0	0	0	0	0	0	0	0	
E. Myelocytes	0	0	0	0	0	0	0	0	0	0	
B. Myelocytes	0	0	0	0	0	0	0	0	0	0	
Myeloblasts	3	1.0%	2	0.66%	1	0.33%	4	1.33%	11	3.33%	
Smudges	0	0	0	0	4	1.33%	4	1.33%	11	2.66%	
Platelets	Markedly diminished.	Markedly diminished.	Markedly diminished.	Markedly diminished.	Markedly diminished.	Practically absent.					
Nucleated R. B. C.	0	1—Normoblast, 1	0	0	0	0	0	0	4—Megaloblast, 4		
	Marked anisocytosis.	Marked anisocytosis.	Moderate anisocytosis.	Moderate anisocytosis.	Moderate anisocytosis.	Marked anisocytosis.			Marked anisocytosis.		
	Marked poikilocytosis.	Marked poikilocytosis.	Moderate poikilocytosis.	Moderate poikilocytosis.	Moderate poikilocytosis.	Slight poikilocytosis.			Slight poikilocytosis.		
Basophilia	Slightly diffused and punctate.	Slightly diffused and punctate.	Slightly diffused.	Slightly diffused.	Slightly diffused.	Slightly diffused.			Slightly diffused.		
No. Cells Counted and %	300	99.92	300	99.95	300	99.91	300	99.97	300	99.93	
Hb.	44%	51%	53%	55%	57%	58%			58%		
R. B. C.	2,680,000	3,048,000	2,632,000	2,706,000	3,864,000				3,864,000		
W. B. C.	2,600	3,100	3,400	3,040	3,400				3,400		
C. I.	1.1	.85	1.0	1.0	1.0				.76		
Condition of Patient	No chill; no fever.	No chill; no fever.	Slight fever.	Slight fever.	No chill; no fever.				No chill; no fever.		
Blood Obtained	Little finger right hand.	Third finger right hand.	Little finger right hand.	Third finger right hand.	Little finger right hand.				Little finger right hand.		Pt. transfused slowly in left arm.

BLOOD CHART—CASE 5

PATIENT'S NAME, BAILEY, IRWIN; WARD M; AGE, 30; MEDICAL NO. 121999; DIAGNOSIS, PERNICIOUS ANEMIA; TRANSFUSION 650 C. C.;

2D (1ST TRANSFUSION 12-15-17, 500 C. C.; WASHED CELLS)

Date	12-18-17		12-18-17		12-18-17		12-18-17		12-19-17		Remarks
Time	Before Transfusion 2.30 p. m.		After Transfusion 3.45 p. m.		5.45 p. m.		8.45 p. m.		2.30 p. m.		
	I		II		III		IV		V		
P. M. N.	189	63.0%	217	72.3%	257	83.3%	241	80.3%	267	89.0%	
P. M. E.	1	0.33%	2	0.66%	0	0	0	0	2	0.66%	
P. M. B.	0	0	0	0	0	0	0	0	1	0.33%	
P. Lym.	28	9.33%	10	3.33%	3	1.0%	2	0.66%	3	1.0%	
S. Lym.	68	22.6%	68	22.6%	37	12.3%	50	16.6%	24	8.0%	
L. Mono.	2	0.66%	0	0	0	0	0	0	0	0	
Transitional	2	0.66%	1	0.33%	1	0.33%	0	0	1	0.33%	
N. Myelocytes	
E. Myelocytes	
B. Myelocytes	
Myeloblasts	
Smudges	10	3.33%	2	0.66%	2	0.66%	6	2.0%	3	1.0%	
Platelets	Markedly decreased, large in size.										
Nucleated R. B. C.	5—Megaloblasts, 2 Normoblasts, 3		3—Normoblast, 3		0		0		0		
Basophilia	Microcytes and macrocytes, Megalocytes. Slightly diffused and occasional punctate.		Microcytes and macrocytes, Megalocytes. Slightly diffused.		Microcytes and macrocytes, Megalocytes. Slightly diffused.		Microcytes and macrocytes, Megalocytes. Slightly diffused.		Microcytes and macrocytes, Megalocytes. Slightly diffused and punctate.		
No. Cells Counted and %	Anisocytosis. Poikilocytosis. 300 99.91		Marked anisocytosis. Marked poikilocytosis. 300 99.95		Marked anisocytosis. Marked poikilocytosis. 300 99.99		Marked anisocytosis. Marked poikilocytosis. 300 99.99		Marked anisocytosis. Marked poikilocytosis. 300 99.99		
Hb.	Estimated (Sahli). 3%		13%		20%		23%		23%		
R. B. C.	480,000		1,360,000		1,456,000		1,324,000		1,312,000		
W. B. C.	5,080		5,640		5,960		6,700		4,390		
C. I.	0.37		0.47		0.71		0.84		0.88		
Condition of Patient	No chill; no fever.		No chill; slight fever.		Slight fever.		Slight fever.		Slight fever.		
Blood Obtained	Little finger right hand.		Third finger right hand.		Little finger right hand.		Third finger right hand.		Little finger right hand. Blood transfused in		

BLOOD CHART—CASE 6

PATIENT'S NAME, CROCKETT; WARD G; AGE, 65; MEDICAL NO. 120650; DIAGNOSIS, PERNICIOUS ANEMIA; TRANSFUSION, 500 C. C.

Date	10-22-17 Before Transfusion 11.45 a. m.	10-22-17 After Transfusion 12.40 p. m.	10-22-17 2.40 p. m.	10-22-17 5.40 p. m.	10-23-17 11.45 a. m.	Remarks					
	I	II	III	IV	V						
P. M. N.	108	36.0%	98	32.6%	212	70.6%	238	79.3%	108	36.0%	
P. M. E.	3	1.0%	1	0.33%	2	0.66%	0	0	3	1.0%	
P. M. B.	1	0.33%	0	0	0	0	0	0	4	1.33%	
L. Lym.	75	25.0%	60	20.0%	15	5.0%	14	4.66%	46	15.3%	
S. Lym.	79	26.3%	100	33.3%	53	17.6%	32	10.6%	77	25.6%	
L. Mono.	4	1.33%	1	0.33%	0	0	0	0	1	0.33%	
Transitional	4	1.33%	3	1.0%	3	1.0%	3	1.0%	5	1.66%	
N. Myelocytes	2	0.66%	2	0.66%	0	0	
E. Myelocytes	0	0	
B. Myelocytes	0	0	
Myeloblasts	1	0.33%	
Smudges	24	8.0%	85	11.6%	14	4.66%	13	4.33%	23	18.3%	
Platelets	Normal; large in size.	Normal; large in size.	Increased; large in size.	Increased; large in size.	Increased; large in size.	Normal; large in size.			Normal; large in size.		
Nucleated R. B. C.	8—Microblasts, 3 Normoblasts, 5 Many microcytes and macrocytes.	18—Microblasts, 4 Normoblasts, 14 Many microcytes and macrocytes.	13—Microblasts, 3 Normoblasts, 9 Intermediate, 1 Few microcytes and macrocytes.	5—Microblasts, 1 Normoblasts, 3 Intermediate, 1 Few microcytes and macrocytes.	6 Microblasts, 1 Normoblasts, 1 Intermediate, 2 Diffused and punctate.	6 Microblasts, 3 Normoblasts, 1 Intermediate, 2 Diffused and punctate.			6 Microblasts, 3 Normoblasts, 1 Intermediate, 2 Diffused and punctate.		
Basophilia	Markedly diffused and punctate.	Markedly diffused and punctate.	Markedly diffused and punctate.	Markedly diffused and punctate.	Markedly diffused and punctate.	Diffused and punctate.			Diffused and punctate.		
	Marked anisocytosis.	Marked anisocytosis.	Slight anisocytosis.	Slight anisocytosis.	Slight anisocytosis.	Slight anisocytosis.			Slight anisocytosis.		
No. Cells Counted and %	300	99.95	300	99.85	300	99.85	300	99.89	300	99.85	
Hb.	20%	35%	34%	39%	32%	31%			31%		
R. B. C.	1,176,000	1,432,000	1,592,000	1,856,000	1,856,000	1,368,000			1,368,000		
W. B. C.	6,000	6,320	7,800	7,840	7,840	8,200			8,200		
C. I.	0.90	1.2	1.1	0.88	1.1	1.1			1.1		
Condition of Patient	No chill; no fever.	No chill; no fever.	No chill; no fever.	No chill; no fever.	No chill; no fever.	No chill; no fever.			No chill; no fever.		
Blood Obtained	Little finger left hand.	Third finger left hand.	Little finger left hand.	Third finger left hand.	Third finger left hand.	Little finger left hand.			Little finger left hand.		Blood transfused in right arm, slowly, then rapidly.

BLOOD CHART—CASE 7

PATIENT'S NAME, WHITE; WARD F; AGE, 50; MEDICAL No., 122613; DIAGNOSIS, PERNICIOUS ANEMIA; 2D TRANSFUSION, 600 C. C.
(1ST TRANSFUSION, 2-3-18)

Date	2-17-18 Before Transfusion 10:45 a. m.	2-17-18 After Transfusion 12:20 a. m.	2-17-18 2:20 p. m.	2-17-18 5:25 p. m.	2-18-18 10:45 a. m.	Remarks
	I	II	III	IV	V	
P. M. N.	100	46.6%	161	33.6%	246	74.0%
P. M. E.	0	0	3	1.6%	0	0
P. M. B.	0	0	0	0	0	0
L. I.	6	2.6%	0	0	1	0.3%
S. I.	129	41.8%	84	28.8%	50	16.9%
T. M.	1	1.6%	11	3.6%	6	2.0%
Transitional	8	2.6%	11	3.6%	8	2.6%
N. Myelocytes	0	0	4	1.3%	8	2.6%
E. Myelocytes	0	0	0	0	0	0
B. Myelocytes	0	0	0	0	0	0
Megakaryocytes	0	0	0	0	0	0
Stragles	12	4.0%	17	5.6%	3	1.0%
Plasma	Decreased moderate.	Decreased slightly, some very large.	Normal.	Some large in size.	Markedly decreased.	Normal, some large in size.
Nucleated R. B. C.	2 Normoblasts.	Intermediate, 1	Normoblast, 21	Intermediate, 6	Normoblast, 1	Normoblast, 7
Basophils	Slightly debased, slight anisocytosis, slight poikilocytosis.	Diffused and punctate. Slight anisocytosis. Slight poikilocytosis.	Slightly debased and punctate. Slight anisocytosis.	Slightly debased and punctate. Moderate anisocytosis. Moderate poikilocytosis.	Slightly debased and punctate. Moderate anisocytosis. Moderate poikilocytosis.	Slightly debased and punctate. Moderate anisocytosis. Moderate poikilocytosis.
No. Cells Counted and %	300	35% 98.92	300	44% 99.70	300	49% 99.97
Hb.	1,288,000	2,181,000	2,640,000	2,748,000	2,418,000	2,537,000
R. B. C.	3,720	2,760	2,400	3,960	3,090	3,030
W. B. C.	1.4	1.0	0.88	0.85	1.0	1.0
Condition of Patient	No chill; no fever.	No chill; no fever.	Severe chill; fever.	Fever.	No chill; no fever.	No chill; no fever.
Blood Obtained	Little finger right hand.	Third finger right hand.	Little finger right hand.	Third finger right hand.	Little finger right hand.	Blood transfused slowly in left arm.

BLOOD CHART—CASE 8

PATIENT'S NAME, HOPKINS; WARD M; AGE, 52; MEDICAL No., 121133; DIAGNOSIS, BANTI'S DISEASE; TRANSFUSION, 400 C. C.
(1ST TRANSFUSION, 500 C. C.) (SAME DONOR AS 1ST)

Date	11-22-17 Before Transfusion 10:40 a. m.	11-22-17 After Transfusion 11:45 a. m.	11-22-17 1:45 p. m.	11-22-17 5:45 p. m.	11-23-17 10:40 a. m.	Remarks
	I	II	III	IV	V	
P. M. N.	200	68.6%	193	64.3%	117	72.3%
P. M. E.	0	0	6	2.6%	13	5.0%
P. M. B.	0	0	0	0	0	0
L. I.	2	1.3%	9	3.6%	7	2.8%
S. I.	14	6.8%	29	13.6%	4	1.6%
T. M.	4	2.6%	4	1.6%	13	4.0%
Transitional	13	4.3%	17	6.5%	8	3.0%
N. Myelocytes	1	0.3%	18	6.5%	11	4.3%
E. Myelocytes	0	0	0	0	0	0
B. Myelocytes	0	0	0	0	0	0
Megakaryocytes	0	0	0	0	0	0
Stragles	0	0	0	0	0	0
Plasma	Increased, large in size.	Increased; large in size.	Increased, markedly enlarged in size.	Greatly increased.	Increased.	Increased.
Nucleated R. B. C.	0	0	0	0	0	0
Basophils	Diffused.	Diffused.	Diffused.	Diffused.	Diffused.	Diffused.
Neutrophils	Marked anisocytosis. Marked poikilocytosis.	Marked anisocytosis. Marked poikilocytosis.	Marked anisocytosis. Marked poikilocytosis.	Marked anisocytosis. Marked poikilocytosis.	Marked anisocytosis. Marked poikilocytosis.	Marked anisocytosis. Marked poikilocytosis.
No. Cells Counted and %	300	99.97	300	99.98	300	99.98
Hb.	3,488,000	3,384,000	3,384,000	3,486,000	4,352,000	4,352,000
R. B. C.	11,560	11,380	10,380	10,640	18,940	18,940
W. B. C.	0.45	0.57	0.57	0.57	0.44	0.44
Condition of Patient	Good; no fever; no chill.	No chill; no fever.	Slight fever.	Slight fever.	No chill; no fever.	No chill; no fever.
Blood Obtained	Little finger right hand.	Third finger right hand.	Third finger right hand.	Third finger right hand.	Little finger right hand.	Blood transfused in left arm, rapidly.

BLOOD CHART—CASE 9

PATIENT'S NAME, THOMAS HOPKINS; WARD M; AGE, 52; MEDICAL No., 121133; DIAGNOSIS, BANTI'S DISEASE (?); TRANSFUSION, 500 C. C.

Date	11-9-17 Before Transfusion 11:20 a. m.	11-9-17 After Transfusion 1:35 p. m.	11-9-17 5:00 p. m.	11-9-17 5:55 p. m.	11-10-17 11:20 a. m.	Remarks
	I	II	III	IV	V	
P. M. N.	200	76.6%	280	73.3%	311	81.3%
P. M. E.	0	0	0	0	0	0
P. M. B.	0	0	0	0	0	0
L. I.	4	1.3%	6	2.0%	7	2.3%
S. I.	1	0.3%	2	0.6%	1	0.3%
T. M.	90	8.6%	17	5.6%	11	3.6%
N. Myelocytes	0	0	0	0	0	0
E. Myelocytes	0	0	0	0	0	0
B. Myelocytes	0	0	0	0	0	0
Megakaryocytes	0	0	0	0	0	0
Stragles	0	0	0	0	0	0
Plasma	Increased markedly.	Increased markedly.	Increased markedly.	Increased greatly, large in size.	Increased.	Increased.
Nucleated R. B. C.	0	0	0	0	0	0
Basophils	Diffused.	Diffused.	Diffused.	Diffused.	Diffused.	Diffused.
Neutrophils	Marked anisocytosis. Marked poikilocytosis.	Marked anisocytosis. Marked poikilocytosis.	Marked anisocytosis. Marked poikilocytosis.	Marked anisocytosis. Marked poikilocytosis.	Marked anisocytosis. Marked poikilocytosis.	Marked anisocytosis. Marked poikilocytosis.
No. Cells Counted and %	300	99.97	300	99.94	300	99.98
Hb.	3,488,000	3,384,000	3,384,000	3,486,000	4,352,000	4,352,000
R. B. C.	11,560	11,380	10,380	10,640	18,940	18,940
W. B. C.	0.45	0.57	0.57	0.57	0.44	0.44
Condition of Patient	Good; no fever; no chill.	No chill; no fever.	Slight fever.	Slight fever.	No chill; no fever.	No chill; no fever.
Blood Obtained	Little finger right hand.	Little finger right hand.	Little finger right hand.	Third finger right hand.	Little finger right hand.	Pt. had no reaction after transfusion except fever of 100°. Blood transfused in left arm, rapidly.

BLOOD CHART—CASE 10

PATIENT'S NAME, PETER SKAFIDOS; WARD F; AGE, 24; MEDICAL No., 120804; DIAGNOSIS, ECHINOCOCCUS CYST OF RIGHT LUNG;
TRANSFUSION, 500 c. c.

Date	10-25-17 Before Transfusion 2.45 p. m.	10-25-17 After Transfusion 3.15 p. m.	10-25-17 5.30 p. m.	10-25-17 Before Operation 3.15 p. m.	10-25-17 After Operation (18 hrs.) 3.30 p. m.	10-26-17 After Operation (18 hrs.) 3.30 p. m.	Remarks				
Time	I	II	III	IV	V	V					
P. M. N.	228	76.0%	227	75.9%	246	82.0%	247	82.3%	251	83.6%	Port died from hem-
P. M. E.	5	1.66%	1	0.33%	1	0.33%	0	0	0	0	orrhage on 10-31-17.
P. M. B.	2	0.66%	2	0.66%	1	0.33%	3	1.0%	2	0.66%	
L. Lym.	27	9.0%	14	4.66%	14	3.33%	14	4.66%	5	1.66%	
S. Lym.	27	9.0%	16	5.33%	18	6.0%	19	6.33%	9	3.0%	
L. Mono.	5	1.66%	3	1.0%	6	2.0%	6	2.0%	6	2.0%	
Transf.	17	5.66%	17	5.66%	9	3.0%	14	4.66%	16	5.33%	Cell seen in slide III
E. Myelocytes	classified here.
E. Myelocytes	
E. Myelocytes	
E. Myeloblasts	
Smudges	8	2.66%	20	6.66%	9	3.0%	6	2.0%	11	3.66%	
Platelets	Normal.	0	Normal.	0	Increased.	0	Increased slightly.	0	Increased slightly.	0	
Nucleated R. B. C.	Diffused very little.	0	Diffused very little.	0	Diffused very little.	0	Diffused very little.	0	Diffused very little.	2	
Reticul.	300	99.96	300	99.90	300	99.99	300	99.95	300	99.91	
No. Cells Counted and %.											
Hb.	25%		35%		35%		33%		32%		
R. B. C.	1,896,000		2,184,000		2,486,000		2,160,000		2,776,000		
W. B. C.	10,560		12,640		13,080		14,800		20,120		
C. I.69		.83		.73		.78		.59		
Condition of Patient	Small hemiplegia and blood-streaked sputum.	Small hemiplegia and blood-streaked sputum.	Small hemiplegia and blood-streaked sputum.	Small hemiplegia and blood-streaked sputum.	Small hemiplegia and blood-streaked sputum.	Small hemiplegia and blood-streaked sputum.	Small hemiplegia and blood-streaked sputum.	Small hemiplegia and blood-streaked sputum.	Fever. Some "old" blood-streaked sputum.		
Blood Obtained	Little finger right hand.	Third finger right hand.	Little finger right hand.	Third finger right hand.	Little finger right hand.	Third finger right hand.	Little finger right hand.	Little finger right hand.	Blood transfused in left arm, somewhat rapidly.		

BLOOD CHART—CASE 11

PATIENT'S NAME, SYLVIA McMILLIAN; WARD O; AGE, 26; GYN. No., 122424; DIAGNOSIS, POST-OPERATIVE; TRANSFUSION, 300 c. c.

Date	1-13-18		1-13-18		1-13-18				Remarks
Time	Before Transfusion 10.00 a. m.		After Transfusion 1.00 p. m.		3.00 p. m.				
	I		II		III		IV		
P. M. N.	227	75.6%	126	42.0%	210	70.0%			To rt. arm was used and had to cut down on vein. Pa- tient died at 4.00 p. m.
P. M. E.	1	0.33%	0	0	0	0			
P. M. B.	0	0	0	0	0	0			
L. Jvm.	0	0	3	1.0%	3	1.0%			
S. Jvm.	29	8.66%	84	28.0%	42	14.0%			
L. Mono.	2	0.66%	6	2.0%	3	1.0%			
Transitional	12	4.0%	15	5.0%	6	2.0%			
N. Myelocytes	6	2.0%	42	14.0%	30	10.0%			
E. Myelocytes	0	0	0	0	0	0			
B. Myelocytes	1	0.33%	0	0	0	0			
Myeloblasts	0	0	3	1.0%	3	1.0%			
Platelets	22	7.33%	21	7.0%	3	1.0%			
Nucleated R. B. C.	Practically absent. 144—Normoblast, 144		Practically absent. 1329—Normoblasts, 1000 Intermediate, 329		Moderately diminished. 849—Normoblasts, 809 Intermediates, 40				
Basophilia	Markedly diffuse; slightly punctate. Moderate anisocytosis. Moderate poikilocytosis.		Markedly diffuse; slight- ly punctate. Moderate anisocytosis. Moderate poikilocytosis.		Markedly diffused; slight punctate. Moderate anisocytosis. Moderate poikilocytosis.				
No. Cells Counted and %.	300		300		300				
Hb.	57%		22%		19%				
R. B. C.	1,112,000		1,216,000		2,480,000				
W. B. C.	37,700		26,360		24,600				
C. I.	0.22		0.91		0.59				
Condition of Patient	Fever.		Fever.		Fever.				
Blood Obtained	Little finger left hand.		Third finger left hand.		Little finger left hand.				

BLOOD CHART—CASE 12

PATIENT'S NAME, CHARLES THOMAS; WARD D; AGE, 43; SURGICAL No., 121146; DIAGNOSIS, SINUS TRACT IN OLD WOUND; TRANSFUSION, 500 c. c.

Date	11-25-17 Before Transfusion 12.00 m.	11-25-17 After Transfusion 2.00 p. m.	11-25-17 4.00 p. m.	11-25-17 7.00 p. m.	11-26-17 12.15 p. m.	Remarks			
Time	I	II	III	IV	V				
P. M. N.	258	80.0%	253	84.3%	250	83.3%	212	80.6%	Pt. was operated on Sept. 20, 1917, for gastric ulcer.
P. M. E.	0	0	0	0	0	0	0	0	" " blood ulcer.
P. M. B.	0	0	0	0	0	0	0	0	" c. c. gastro intestinal.
L. Iywn.	3	1.0%	1	0.33%	2	0.66%	1	0.33%	when needle became closed; interval of half hour before continuing.
S. Iywn.	14	4.66%	10	3.33%	13	4.0%	9	3.0%	Seen in slide I.
L. Mono.	2	0.66%	1	0.33%	0	0	3	1.0%	Classified under Trans.
Transitional	9	3.0%	4	1.33%	4	1.33%	6	2.0%	Pt. was operated on again on Nov. 28, 1917. Found tubercles throughout abdominal cavity. Pt. died on Nov. 29, 1917.
X. Myelocytes	
E. Myelocytes	
B. Myelocytes	
Mycoblasts	
Smudges	14	4.66%	31	10.3%	30	10.0%	20	6.66%	
Platelets	Normal.	Slightly increased.	Slightly increased.	Slightly increased.	Greatly increased.	Greatly increased.	Greatly increased.	Greatly increased.	
Nucleated R. B. C.	Slight anisocytosis. Slight poikilocytosis.	Slight anisocytosis. Slight poikilocytosis.	Slight anisocytosis. Slight poikilocytosis.	Slight anisocytosis. Slight poikilocytosis.	Slight anisocytosis. Slight poikilocytosis.	Slight anisocytosis. Slight poikilocytosis.	Slight anisocytosis. Slight poikilocytosis.	Slight anisocytosis. Slight poikilocytosis.	
Rosophilia	0	0	0	Diffused.	0	0	0	0	
No. Cells Counted and %.	300	99.58	300	99.92	300	99.95	300	99.91	
Hb. B. C.	43%	53%	53%	53%	53%	53%	53%	52%	
R. B. C.	3,144,000	3,296,000	3,696,000	3,656,000	3,656,000	4,288,000	4,288,000	4,288,000	
W. B. C.	17,280	14,640	12,160	14,500	14,500	11,520	11,520	11,520	
C. L.	0.72	0.82	0.72	0.73	0.73	0.61	0.61	0.61	
Condition of Patient	No chill; no fever.	Slight chill.	No chill; no fever.	No chill; no fever.	No chill; no fever.	No chill; no fever.	No chill; no fever.	No chill; no fever.	
Blood Obtained	Little finger right hand.	Third finger right hand.	Little finger right hand.	Third finger right hand.	Third finger right hand.	Little finger right hand.	Left arm, slowly.	Blood transfused in left arm, slowly.	

BLOOD CHART—CASE 13

PATIENT'S NAME, M. STRZYKOWSKI; WARD G; AGE, 14; MEDICAL No. 120599; DIAGNOSIS, TYPHOID FEVER; TRANSFUSION, 300 C. C. (10-8-17 1ST TRANSFUSION, 400 C. C.)

Date	10-11-17	10-11-17	10-11-17	10-11-17	10-12-17	Remarks
Time	Before Transfusion 12 m.	After Transfusion 1.50 p. m.	3.15 p. m.	6.15 p. m.	11.15 p. m.	
	I	II	III	IV	V	
P. M. N.	138	46.0%	167	55.0%	186	62.0%
P. M. E.	4	1.33%	0	0	1	0.33%
P. M. B.	0	0	0	0	0	0
L. I. cells	56	18.6%	31	10.3%	29	11.0%
S. Lym.	70	23.3%	65	21.6%	47	18.0%
L. Mono.	2	0.66%	5	1.66%	7	2.8%
Transitional	17	5.66%	7	2.33%	13	4.33%
N. Myelocytes
E. Myelocytes
B. Myelocytes
Myeloblasts
Smudges	13	4.33%	25	8.33%	8	3.0%
Platelets	Decreased slightly;	Large normal; large.	Decreased; large in size.	Large in size.	Decreased; large in size.	
Nucleated R. B. C.	0	0	0	0	0	
Resophilia	Diffused and anisocytosis.	Diffused.	Diffused.	Diffused.	Diffused.	
No. Cells Counted and %	300	99.88	300	99.88	300	99.82
Hb.	38%	40%	40%	40%	40%	
R. B. C.	1,872,000	1,698,000	2,168,000	2,376,000	2,392,000	
W. B. C.	2,329	3,760	5,300	3,640	3,240	
C. I.	0.91	1.2	0.93	0.87	0.91	
Condition of Patient	Slight fever.	Slight fever.	Slight fever.	Fever.	Slight fever.	
Blood Obtained	Little finger left hand.	Third finger left hand.	Third finger left hand.	Second finger left hand.	Third finger left hand.	Blood transfused in left arm, very slowly.

BLOOD CHART—CASE 14

PATIENT'S NAME, MARIE ZAHBODKA; WARD G; AGE, 29; MEDICAL No. 120464; DIAGNOSIS, TYPHOID FEVER; TRANSFUSION, 250 C. C.

Date	10-10-17	10-10-17	10-10-17	10-10-17	10-11-17	Remarks
Time	Before Transfusion 11.00 a. m.	After Transfusion 12.05 p. m.	2.00 p. m.	5.30 p. m.	11.30 a. m.	
	I	II	III	IV	V	
P. M. N.	98	32.6%	150	50.0%	154	51.3%
P. M. E.	2	0.6%	1	0.33%	0	0
P. M. B.	0	0	0	0.33%	0	0
L. I. cells	40	13.0%	46	15.3%	62	20.7%
S. Lym.	122	40.6%	66	22.0%	36	12.0%
L. Mono.	5	1.6%	2	0.66%	3	1.0%
Transitional	15	5.0%	29	9.6%	21	7.0%
N. Myelocytes
E. Myelocytes
B. Myelocytes
Myeloblasts
Smudges	12	4.0%	12	4.0%	15	5.0%
Platelets	Large in size; decreased.	Large in size; decreased.	Large in size; decreased.	Large in size; decreased.	Slightly increased.	
Nucleated R. B. C.	None.	None.	None.	None.	None.	
Resophilia	Diffused and punctate.	Diffused.	Diffused; very few.	Diffused and punctate; few.	Diffused; few.	
No. Cells Counted and %	300	99.7	300	99.83	300	99.86
Hb.	38%	38%	40%	39%	38%	
R. B. C.	2,128,000	1,768,000	1,648,000	1,872,000	2,384,000	
W. B. C.	5,560	7,440	6,120	5,560	5,380	
C. I.	0.71	1.1	1.2	1.0	0.82	
Condition of Patient	Slight chill.	Chill.	Fever.	Fever.	Slight fever.	
Blood Obtained	Little finger right hand.	Third finger right hand.	Third finger right hand.	Little finger right hand.	Little finger right hand.	Blood transfused in left arm—rapidly.

BLOOD CHART—CASE 15

PATIENT'S NAME, BAUER; WARD G; AGE, 28; MEDICAL No. 125383; DIAGNOSIS, BENZOL POISONING; TRANSFUSION, 600 C. C.

Date	5-20-18	5-20-18	5-20-18	5-21-18	5-21-18	Remarks
Time	Before Transfusion 3.15 p. m.	After Transfusion 4.10 p. m.	6.10 p. m.	9.10 p. m.	3.15 p. m.	
	I	II	III	IV	V	
P. M. N.	50	16.0%	62	20.0%	95	31.0%
P. M. E.	2	0.66%	0	0	2	0.66%
P. M. B.	0	0	0	0	0	0
L. I. cells	1	0.33%	8	2.66%	0	0
S. Lym.	26	78.6%	162	64.0%	167	64.0%
L. Mono.	5	1.6%	10	3.33%	10	3.33%
Transitional	5	1.6%	10	3.33%	4	1.33%
N. Myelocytes
E. Myelocytes
B. Myelocytes
Myeloblasts
Smudges	2	0.66%	2	0.66%	2	0.66%
Platelets	Practically absent.	Practically absent.	Practically absent.	Practically absent.	Practically absent.	
Nucleated R. B. C.	2—Normoblast, 1	0	0	0	2—Normoblasts.	
Resophilia	Slightly diffused and punctate.	Slightly diffused and punctate.	Slightly diffused and punctate.	Slightly diffused and punctate.	Slightly diffused and punctate.	
No. Cells Counted and %	300	99.91	300	99.98	300	99.98
Hb.	45%	45%	47%	45%	45%	
R. B. C.	1,994,000	1,768,000	2,706,000	2,706,000	2,376,000	
W. B. C.	1,190	2,640	3,220	1,080	1,080	
C. I.	1.0	1.2	1.0	0.83	0.95	
Condition of Patient	No chill; no fever.	No chill; no fever.	Slight fever.	Slight fever.	Slight fever.	
Blood Obtained	Little finger left hand.	Third finger left hand.	Little finger left hand.	Third finger left hand.	Little finger left hand.	Pt. transfused slowly

BLOOD CHART—CASE 16

PATIENT'S NAME, CHAS. WEBER; WARD F; AGE, 17; MEDICAL NO., 122256; DIAGNOSIS, BENZOL POISONING; TRANSFUSION, 275 C. C.

Date	1-11-18	1-1-18	1-1-18	1-1-18	1-2-18	Remarks
Time	Before Transfusion 10.00 a. m.	After Transfusion 11.30 a. m.	1.30 p. m.	4.30 p. m.	11.30 a. m.	
	I	II	III	IV	V	
P. M. N.	121	143	166	138	119	
P. M. E.	6	6	8	4	5	
P. M. B.	0	0	0	0	0	
L. Lym.	60	47	28	7	20	
S. Lym.	68	71	86	131	128	
L. Mono.	3	4	0	6	5	
Transitional	31	23	8	8	21	
N. Myelocytes	
E. Myelocytes	
B. Myelocytes	
Myeloblasts	
Smudges	11	0	1	6	2	
Platelets	Practically absent.	Practically absent.	Practically absent.	Practically absent.	Practically absent.	
Nucleated R. B. C.	0	0	0	0	300	
Rasophilia	Slightly diffused.	Slightly diffused.	Slightly diffused.	Slightly diffused.	Slightly diffused.	
No. Cells Counted and %	300	300	300	300	300	
Hb.	54%	59%	57%	57%	54%	
R. B. C.	2,648,000	2,272,000	2,512,000	3,215,000	2,368,000	
W. B. C.	2,400	3,160	1,880	1,800	1,720	
C. I.	1.03	1.3	1.9	0.89	1.1	
Condition of Patient	No chill; no fever.	No chill; no fever.	Slight fever.	Slight fever.	No chill; no fever.	
Blood Obtained	Little finger right hand.	Third finger right hand.	Little finger right hand.	Third finger right hand.	Little finger right hand.	Blood transfused in left arm slowly.

BLOOD CHART—CASE 17

PATIENT'S NAME, CHAS. WEBER; WARD F; AGE, 17; MEDICAL NO., 122256; DIAGNOSIS, BENZOL POISONING; THIRD TRANSFUSION, 300 C. C.

Date	1-9-18	1-9-18	1-9-18	1-9-18	1-10-18	Remarks
Time	Before Transfusion 2.00 p. m.	After Transfusion 4.00 p. m.	6.00 p. m.	9.00 p. m.	2.00 p. m.	
	I	II	III	IV	V	
P. M. N.	96	110	111	90	90	
P. M. E.	1	1	1	1	3	
P. M. B.	0	0	0	0	1	
L. Lym.	32	18	11	13	17	
S. Lym.	115	129	127	162	130	
L. Mono.	16	7	11	8	14	
Transitional	28	28	23	18	37	
N. Myelocytes	1	0	5	1	1	
E. Myelocytes	0	0	0	0	0	
B. Myelocytes	0	0	0	0	0	
Myeloblasts	0	1	0	0	0	
Smudges	11	6	11	6	7	
Platelets	Practically absent; those seen large in size.	Practically absent; those seen large in size.	Practically absent; those seen large in size.	Practically absent.	Practically absent.	
Nucleated R. B. C.	0	0	0	0	1	
Rasophilia	Moderately diffused.	Moderately diffused.	Moderately diffused.	Moderately diffused.	Moderately diffused.	
No. Cells Counted and %	300	300	300	300	300	
Hb.	39%	42%	43%	40%	41%	
R. B. C.	2,232,000	2,704,000	2,732,000	2,120,000	2,395,000	
W. B. C.	1,920	2,680	2,080	1,880	1,840	
C. I.	0.88	0.77	0.79	0.90	0.93	
Condition of Patient	No chill; no fever.	No chill; no fever.	Slight chill; slight fever.	Slight fever.	No chill; no fever.	
Blood Obtained	Little finger right hand.	Third finger right hand.	Little finger right hand.	Third finger right hand.	Little finger right hand.	Blood transfused in left arm slowly.

Many patho. lym. in I, II, V.

BLOOD CHART—CASE 18

PATIENT'S NAME, ELLEN FOPPIO; WARD G; AGE, 36; MEDICAL NO., 125109; DIAGNOSIS, BENZOL POISONING; TRANSFUSION, 750 C. C.

Date	5-11-18	5-11-18	5-11-18	5-11-18	5-12-18	Remarks
Time	Before Transfusion 2.00 p. m.	After Transfusion 3.45 p. m.	5.45 p. m.	8.45 p. m.	2.00 p. m.	
	I	II	III	IV	V	
P. M. N.	11	14	3	9	11	
P. M. E.	0	2	0	0	0	
P. M. B.	0	0	0	0	0	
L. Lym.	108	48	11	16	12	
S. Lym.	169	223	232	270	277	
L. Mono.	12	9	3	0	0	
Transitional	0	2	0	0	0	
N. Myelocytes	0	0	0	0	0	
E. Myelocytes	0	0	0	0	0	
B. Myelocytes	0	0	0	0	0	
Myeloblasts	0	2	0	5	0	
Smudges	0	0	0	0	0	
Platelets	Practically absent.	Occasional; those seen large in size, bizarre in shape.	Practically absent.	Practically absent.	Practically absent.	
Nucleated R. B. C.	0	0	0	1	0	
Rasophilia	Moderate anisocytosis. Moderate poikilocytosis. Slightly diffused.	Moderate anisocytosis. Moderate poikilocytosis. Slightly diffused.	Moderate anisocytosis. Moderate poikilocytosis. Slightly diffused.	Moderate anisocytosis. Moderate poikilocytosis. Slightly diffused.	Moderate anisocytosis. Moderate poikilocytosis. Slightly diffused.	
No. Cells Counted and %	300	300	300	300	300	
Hb.	35%	46%	44%	45%	40%	
R. B. C.	2,048,000	2,856,000	2,432,000	2,464,000	2,616,000	
W. B. C.	600	640	800	800	280	
C. I.	.87	.82	.91	.93	.76	
Condition of Patient						
Blood Obtained	Little finger left hand.	Third finger left hand.	Little finger left hand.	Third finger left hand.	Little finger left hand.	Pt. transfused slowly in right arm.

BLOOD CHART—CASE 19

PATIENT'S NAME, STROMBERG; WARD G; AGE, 19; MEDICAL No., 126431; DIAGNOSIS, IDIOPATHIC PURPURA; TRANSFUSION, 700 c. c.

Date	Before Transfusion 11:30-18 2.00 p. m.	After Transfusion 4:10-18 3.10 p. m.	4:30-18 3.30 p. m.	4:50-18 3.50 p. m.	5:10-18 4.10 p. m.	Remarks
	I	II	III	IV	V	
P. M. N.	247	247	247	247	247	
P. M. E.	1	1	1	1	1	
P. M. B.	1	1	1	1	1	
L. Ery.	30	30	30	30	30	
S. Lym.	1	1	1	1	1	
L. Mono.	1	1	1	1	1	
Transitional	1	1	1	1	1	
N. Myelocytes	1	1	1	1	1	
E. Myelocytes	1	1	1	1	1	
B. Myelocytes	1	1	1	1	1	
M. Myelocytes	1	1	1	1	1	
Stomatocytes	1	1	1	1	1	
Platelets	Practically absent.	Practically absent.	Practically absent.	Practically absent.	Practically absent.	
Nucleated R. B. C.	0	0	0	0	0	
No. Cells Counted and %	73%	81%	81%	81%	81%	
R. B. C.	5,014,000	5,120,000	5,120,000	5,120,000	5,120,000	
Hb.	2.80	2.80	2.80	2.80	2.80	
W. B. C.	13,400	13,400	13,400	13,400	13,400	
C.	0.75	0.75	0.75	0.75	0.75	
Condition of Patient	No chill; no fever.	No chill; no fever.	Slight fever.	Slight fever.	No chill; no fever.	
Blood Obtained	Little finger right hand.	Third finger right hand.	Third finger right hand.	Third finger right hand.	Little finger right hand.	Pt. transfused slowly

BLOOD CHART—CASE 20

PATIENT'S NAME, MARY STROMBERG; WARD G; AGE, 19; MEDICAL No., 126431; DIAGNOSIS, IDIOPATHIC PURPURA; 1ST TRANSFUSION, 600 c. c.

Date	Before Transfusion 4:30-18 12.30 p. m.	After Transfusion 4:50-18 1.55 p. m.	5:10-18 2.15 p. m.	5:30-18 2.35 p. m.	5:50-18 2.55 p. m.	Remarks
	I	II	III	IV	V	
P. M. N.	196	196	196	196	196	
P. M. E.	1	1	1	1	1	
P. M. B.	1	1	1	1	1	
L. Ery.	4	4	4	4	4	
S. Lym.	66	66	66	66	66	
L. Mono.	9	9	9	9	9	
Transitional	12	12	12	12	12	
N. Myelocytes	0	0	0	0	0	
E. Myelocytes	0	0	0	0	0	
B. Myelocytes	0	0	0	0	0	
M. Myelocytes	0	0	0	0	0	
Stomatocytes	0	0	0	0	0	
Platelets	Practically absent; those seen large in size.	Markedly diminished; those seen large in size and bizarre in shape.	Markedly diminished; those seen large in size and bizarre in shape.	Practically absent; those seen large in size and bizarre in shape.	Practically absent; those seen large in size.	
Nucleated R. B. C.	0	0	0	0	0	
No. Cells Counted and %	800	800	800	800	800	
R. B. C.	3,120,000	3,120,000	3,120,000	3,120,000	3,120,000	
Hb.	7.00	7.00	7.00	7.00	7.00	
W. B. C.	11,680	11,680	11,680	11,680	11,680	
C.	0.62	0.62	0.62	0.62	0.62	
Condition of Patient	No chill; no fever.	No chill; no fever.	Severe chill.	Fever 103°.	No chill; no fever.	
Blood Obtained	Little finger left hand.	Third finger left hand.	Third finger left hand.	Third finger left hand.	Little finger left hand.	Pt. transfused in left arm very slowly

BLOOD CHART—CASE 21

PATIENT'S NAME, WILLIAM MEYER; WARD F; AGE, 52; MEDICAL No., 121243; DIAGNOSIS, HYPERTENSION WITH MYOCARDIAL INSUFFICIENCY; CONTROL; NO TRANSFUSION

Date	Before Transfusion 11:30-17 2.30 p. m.	After Transfusion 11:50-17 4.30 p. m.	12:10-17 4.50 p. m.	12:30-17 5.10 p. m.	Remarks
	I	II	III	IV	
P. M. N.	212	212	212	212	
P. M. E.	1	1	1	1	
P. M. B.	1	1	1	1	
L. Ery.	19	19	19	19	
S. Lym.	1	1	1	1	
L. Mono.	5	5	5	5	
Transitional	11	11	11	11	
N. Myelocytes	0	0	0	0	
E. Myelocytes	0	0	0	0	
B. Myelocytes	0	0	0	0	
M. Myelocytes	0	0	0	0	
Stomatocytes	0	0	0	0	
Platelets	Normal.	Normal.	Normal.	Normal.	
Nucleated R. B. C.	0	0	0	0	
No. Cells Counted and %	74%	74%	74%	74%	
R. B. C.	4,384,000	4,376,000	4,376,000	4,376,000	
Hb.	7.30	7.30	7.30	7.30	
W. B. C.	11,680	11,680	11,680	11,680	
C.	0.84	0.84	0.84	0.84	
Condition of Patient	No chill; no fever.	No chill; no fever.	No chill; no fever.	No chill; no fever.	
Blood Obtained	Little finger right hand.	Third finger right hand.	Third finger right hand.	Third finger right hand.	

ELIZABETH FRY—QUAKER REFORMER¹

By HENRY M. THOMAS

In speaking of Elizabeth Fry to my friends I am struck with how little is known about her, and yet one hundred years ago she was beginning in London a career that made her the most influential woman of her time, certainly in philanthropy and, I believe, in general.

To understand Elizabeth Fry and her struggles it is necessary to know something about Quakers, or the Society of Friends, to which sect she belonged.

Most of you know that the Society of Friends was founded by George Fox in 1647-48 as a protest against the formality and abuses which he believed had affected the Church at that time. He taught that true religion is a direct personal experience, and that there is in every man's soul something that responds to the truth as revealed in the Bible, which, when properly regarded and attended to, is a safe guide for conduct. This view led to a personal interpretation of the Bible and did away with creeds and the authority of priests or ministers. He and his followers "bore testimony," as they would say, against many customs and beliefs that they disapproved of. They took many of the injunctions of the Bible literally and felt it wrong to call any man master and to show more respect to one than to another, and they therefore refused to take off their hats before the great and keep them on before the lowly, said "thee" and "thou" to their equals and superiors as well as to those usually called inferiors, adopted a manner of dress which they did not change with the fashions, refused to take legal oaths, and many other such things. From the first they acknowledged the complete equality of women and gave them equal influence in the conduct of the Society.

George Fox was a powerful, persuasive preacher, and influenced many people particularly among the lowly, but not a few among the well-to-do and learned. Among these latter were William Penn, Robert Barclay and John Gurney. John Gurney, the ancestor of Elizabeth Fry, was put into prison with other Friends and remained there for three years because he would not take the oath of allegiance, his testimony being against taking any oath. All the Gurneys appear to have been prosperous, and were interested in woolen weaving and in banking.

John Gurney, Elizabeth Fry's father, married Catherine Bell, the great granddaughter of Robert Barclay, the Quaker apologist, and so the Gurneys of Earlham could trace their ancestry on both sides through an unbroken line of influential Quakers to founders of the Society.

John Gurney had inherited quite a large property and had himself prospered. In 1786 he leased from Edward Bacon the estate of Earlham in Norfolk near Norwich, and it is

from this estate which stayed in the Gurney family for nearly 100 years that the Gurneys of Earlham took their name.

Augustus Hare's book (*The Gurneys of Earlham*) is by far the most attractive account of this remarkable family. John Gurney and his wife had 12 children, 11 of whom grew up. Of these 11 there were seven daughters and four sons. Mrs. Gurney died when her youngest child was only a little over a year old, and the eldest, Catherine, who from that time took charge of the family, was only 17. Mr. Gurney and his wife were not strict Quakers, and although they conformed in some respects to the customs of the Society, they were very liberal in their manner of life and I have no doubt were the objects of deep concern to their plainer relatives and other members of the Society.

At the time of Mrs. Gurney's death, Elizabeth, the third daughter, was just 12, having been born on the 21st of May, 1780. There was one sister between Catherine and herself and next to her came a boy, John, then four girls born in three years, and three boys ending the flock. These 11 children, deprived of their mother, were drawn closely together and developed themselves and each other into a wonderfully united family. Catherine, who when still very young, was known as Mrs. Catherine Gurney, felt the chief responsibility of their bringing up, and with the help of the older girls guided them as best she could. The father interfered but little, requiring only that they go to Meeting on First Day at least once and sometimes twice. Even this slight conformity was resented by the young people and many are the disparaging remarks recorded in the journals of the children, for keeping of journals appeared to be one of the methods of education in this family, and, indeed, in general at that period. In "*The Gurneys of Earlham*" we find interesting abstracts from these journals and I wish that I might read you some of them. Indeed, I must read one note written by Louisa Gurney when 11 years' old, particularly as it refers to the subject of our study and gives us a glimpse of one phase of the family.

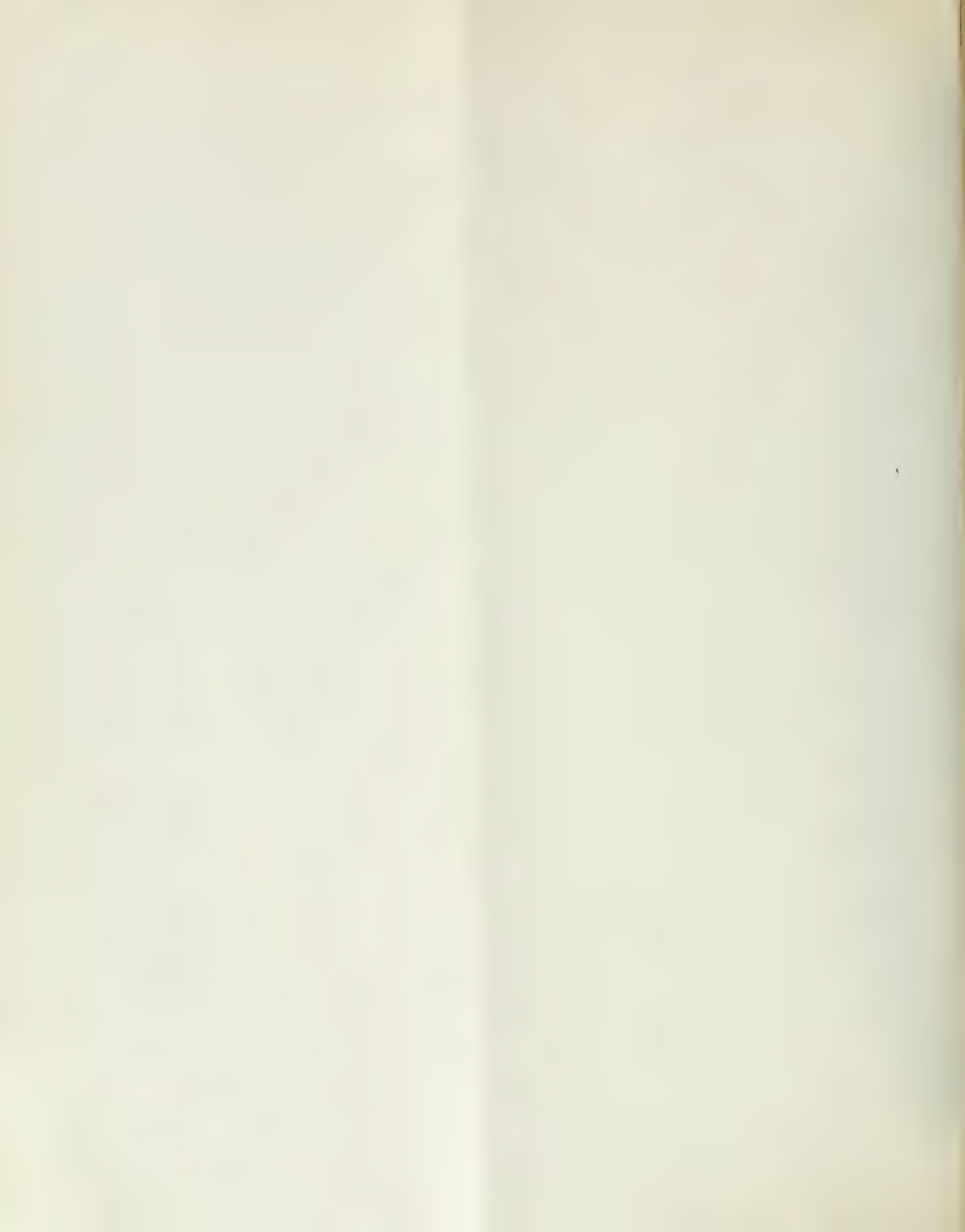
Aug. 14 (1796). Betsy is so ill, I look forward with the most gloomy ideas concerning her. . . . A great many Friends came to tea. I did all I could to please them. How charming it is to feel one is giving pleasure: though I can never say how stupid they were to me. . . . After tea Kitty chose we should work again; this was rather a tug to me, but I bore it pretty well, only Kitty did provoke me by making me give up something to Chenda, merely because she was the eldest; there is nothing I hate so much as this sort of partiality; it does provoke me so. We read a little Sacred History; I like the Old Testament amazingly.

The house at Earlham was very large and the Gurneys entertained freely, and as the girls grew older it must have been a most attractive place to visit. The seven girls dressed as gaily as possible, and were often seen in a band riding

¹ Read before The Johns Hopkins Historical Society, February 12, 1917.



ELIZABETH, MRS. FRY.
After the Portrait by George Richmond



over the country on their ponies, wearing scarlet riding habits. The literary and scientific young men of the neighborhood came to the house and there was much discussion on the subjects of the day, particularly in relation to the philosophy of Rousseau, Voltaire and other free-thinking authors of those times. Among this group there were only two young men who took a serious view of life—one the Baptist minister, the other a Roman Catholic chemist named Pitchford, and strangely enough it was this latter who was the one steadying influence to this flock of Quakers. Among this band Elizabeth was probably the gayest and in many ways the most attractive. She sang sweetly, danced beautifully, and was a remarkably independent character. From a very early age she appears to have been delicate and to have suffered from marked nervous symptoms. She was dreadfully afraid of many things, particularly of the dark and of the water. She also kept a diary, but, unfortunately, when she read it over towards the end of her life she felt it wise to destroy all the early years. Judging from what she wrote later, it would have been a most valuable account of the feelings and experiences of a nervous child. She herself when 48 recorded her impressions of herself at an early age:

Dagenham, Eighth Month, 23d, 1828. My earliest recollections are, I should think, soon after I was two years old; my father at that time had two houses, one in Norwich, and one at Bramerton, a sweet country place, situated on a Common, near a pretty village; here, I believe, many of my early tastes were formed, though we left it to reside at Earham, when I was about five years. The impressions then received remain lively on my recollection; the delight in the beauty and wild scenery in parts of the Common, the trees, the flowers, and the little rills, that abounded on it, the farm houses, the village school, and the different poor people and their cottages; particularly a poor woman with one arm, whom we called one-armed Betsy; another neighbor, Green-grass, and her strawberry beds around a little pond; our gardener, who lived near a large piece of water, and used to bring fish from it; here, I think, my love for the country, the beauties of nature, and attention to the poor, began. My mother was most dear to me, and the walks she took with me in the old-fashioned garden, are as fresh with me, as if only just passed; and her telling me about Adam and Eve being driven out of Paradise: I always considered it must be just like our garden at Bramerton. I remember that my spirits were not strong; that I frequently cried if looked at, and used to say that my eyes were weak; but I remember much pleasure and little suffering, or particular tendency to naughtiness, up to this period. Fear about this time began to show itself, of people and things: I remember being so much afraid of a gun, that I gave up an expedition of pleasure with my father and mother, because there was a gun in the carriage. I was also exceedingly afraid of the dark, and suffered so acutely from being left alone without a light after I went to bed, that I believe my nervous system was injured in consequence of it; also, I had so great a dread of bathing (to which I was at times obliged to submit) that at the first sight of the sea, when we were as a family going to stay by it, it would make me cry; indeed, fear was so strong a principle in my mind, as greatly to mar the natural pleasure of childhood. I am now of opinion, that it would have been much more subdued, and great suffering spared, by its having been still more yielded to; by having a light left in my room; not being long left alone; and never forced to bathe; for I do not at all doubt that it partly arose from that

nervous susceptible constitution, that has at times, throughout my life, caused me such real and deep suffering. I know not what would have been the consequence, had I had any other than a most careful and wise mother, and judicious nurses, or had I been alarmed, as too many children are, by false threats of what might happen.

Even though treated so carefully by others her vivid imagination tormented her, and her early diaries must have contained many outpourings of her spirit. These are lost and we can only guess their character by her later struggles and the records of her sisters and friends.

John Pitchford records¹ that she told him of being so impressed as a child by the story of Abraham and Isaac that she was afraid to go to Meeting for fear that her parents would be required to sacrifice her.

The state of her health secured her many privileges. She was allowed to sleep later than the other children and was usually excused from going to Meeting on Sundays—a much prized privilege. The meeting house in Norwich was reached through Goat's Lane and the children always spoke of the meeting as "Goat's," and recorded in their journals their feelings with such remarks as "I stayed at home from Goat's which I was most glad of," "A long, dis(disgusting) meeting at Goat's," etc. (Louisa, 11 years.)

Mr. Gurney was "labored with" about his indulgence of Elizabeth, and when she was older he required her to attend Meeting more regularly. There were no paid ministers among the Quakers and they depended for the "spoken word" upon certain of their members feeling called; that is, having a sense that they must either pray or preach. Certain members who spoke frequently and acceptably were acknowledged by the Meeting and designated as ministers, and certain of them traveled from Meeting to Meeting and were called Public Friends or Visiting Friends. It was to hear one of these that Elizabeth Gurney went when she was 17 years old. Her diary, which has been preserved from about this time, reads:

Sunday, Feb. 4th, 1798. This morning I went to Meeting, though but poorly, because I wished to hear an American Friend, named William Savery. Much passed there of a very interesting nature. I have had a faint light spread over my mind, at least I believe it is something of that kind, owing to having been much with, and heard much excellence from, one who appears to me a true Christian. It has caused me to feel a little religion. My imagination has been worked upon, and I fear all that I have felt will go off. I fear it now; though at first I was frightened, that a plain Quaker should have made so deep an impression upon me; but how truly prejudiced in me to think that, because good came from a Quaker, I should be led away by enthusiasm and folly. But I hope I am now free from such fears. I wish the state of enthusiasm may last, for to-day I have felt that there is a God; I have been devotional, and my mind has been led away from the follies that it is mostly wrapped up in. We have had much serious conversation; in short, what he said and what I felt, was like a refreshing shower, falling upon earth, that has been dried up for ages. It has not made me unhappy: I have felt ever since

¹ Augustus Hare: Gurneys of Earham, Vol. I, p. 47.

humble. I have longed for virtue. I hope to be truly virtuous; to let sophistry fly from my mind; not to be enthusiastic and foolish; but only to be so far religious as will lead to virtue. There seems nothing so little understood as religion.

A most interesting struggle had begun of which I can only give the bare outlines. She records two days following, on the 6th:

My mind has by degrees flown from religion. I rode to Norwich, and had a very serious ride there; but meeting, and being looked at, with apparent admiration, by some officers, brought on vanity; and I came home as full of the world, as I went to town full of heaven.

However defective the education of the Gurney children may have been; it had at least led to a remarkable independence of thought. Of all of them Elizabeth seems to have been the most independent, and she then and all through her life showed a very clear insight into her thoughts and feelings. She records on Sunday, the 11th:

It is very different to this day week (a day never to be forgotten whilst memory lasts). I have been to Meeting this morning To-day I have all my old irreligious feelings: my object shall be to search, try to do right, and if I am mistaken, it is not my fault; but the state I am now in makes it difficult to act. What little religion I have felt has been owing to my giving way quietly and humbly to my feelings; but the more I reason upon it, the more I get into a labyrinth of uncertainty, and my mind is so much inclined to both scepticism and enthusiasm, that if I argue and doubt, I shall be a total sceptic; if, on the contrary, I give way to it, and as it were, wait for religion, I may be led away. But I hope that will not be the case; at all events, religion, true and uncorrupted, is of all comforts the greatest; it is the first stimulus to virtue; it is a support under every affliction. I am sure it is better to be so in an enthusiastic degree, than not to be so at all, for it is a delightful enthusiasm.

There are many other records of the struggle. She was so determined not to be carried away by her emotions that she got her father's consent to send her to London so that she might see for herself the attractions of the world and decide whether she could be content in their enjoyment. While in London she took music and dancing lessons, went to the plays and to the opera, and saw as much of gay society as her opportunities allowed. Her diary for March 26, 1798, reads:

This morning I went to Amelia Opie's and had a pleasant time. I called on Mrs. Siddons, who was not at home; then on Dr. Batty; then on Mrs. Twiss, who gave me some paint for the evening. I was painted a little, I had my hair dressed, and did look pretty for me. Mr. Opie, Amelia, and I, went to the Opera concert. I own, I do love grand company. The Prince of Wales was there; and I must say, I felt more pleasure in looking at him, than in seeing the rest of the company, or hearing the music. I did nothing but admire his Royal Highness; but I had a very pleasant evening indeed.

On the other side, William Savery was also in London and she went to Meeting to hear him preach and had some conversation with him, and when she returned after two months she began to feel pretty sure that she was going to turn into a plain Quaker. She regarded the change with great interest, but with not a little apprehension, as she knew what a trial it would be to her father as well as to the rest of the children.

In May, to distract her mind, her father proposed another visit to London, and she writes in her journal on the 24th:

I wrote to my father this morning. I must be most careful not to be led by others, for I know at this time I have so great a liking for plain Friends, that my affection being so much engaged, my mind may be also by them. I hope as I now find myself in so wavering a state, that I may judge without prejudice of Barclay's Apology.

It was about this time, when she was just 18, that she began her first independent philanthropic venture—the establishment of her school at Earlham for poor children. She had always found it easy to do for others, and even before her religious awakening she had been her father's instrument for the distribution of his charities. She took such a delight in doing for people and giving help that she recognized very clearly that she deserved no great praise for so doing.

Her development into a plain Quaker progressed deliberately and she took no step in that direction without much thought and travail of spirit, but she adopted one peculiarity after another in spite of the open opposition of her immediate family and often against what seemed to her the dictates of reason. She gave up dancing—a pleasure she delighted in—and singing, gradually changed the manner of her dress, and used thee and thou, the so-called singular form.

To counteract all this Mr. Gurney took her with some of the other children on trips, and she seems to have enjoyed what she saw, but the Quakers whom they met at various places interested her more. She on her part was the object of the deepest interest to the Friends, as indeed was natural.

At one time, when 19, she was appointed on a committee to investigate the Ackworth School, and afterwards, when the young people were encouraged to speak and nothing was said, she spoke. Of this she writes: "As it appeared to me it was delaying the meeting I took courage (as I thought it was more right than wrong to speak); and said what I thought of the grammar and ciphering; I felt glad I had done it though I trembled at doing it not a little." She was then asked her opinion of other matters about the school. This seems to have been her first service on a committee of investigation.

During this visit she records on July 4, 1799: "This morning we walked to York and saw its wonders. We saw the Friends' Retreat for crazy people which my father thought extravagantly kept." This institution had been founded in 1792 by Friends, under the guidance of William Tuke, and was the first place in England where the humane treatment of the insane was attempted. I have found no other references to her having visited it again, but she was doubtless quite familiar with the ideas and methods carried out there, as the proper care of the insane was a common subject of discussion in the Society.

In America the Friends had long been interested in the subject. In 1709 the Philadelphia Monthly Meeting took steps towards the establishment of a hospital for the sick and the insane, but it was not until 1751 that the Pennsylvania

hospital was founded. This institution among other sick cared for patients "distempered in mind and deprived of their mental faculties." In 1813 the Philadelphia Friends, stimulated by the success of the York Retreat, founded at Frankford a Friends' Asylum.

Upon returning to Earlham, Elizabeth began to take a more active part in the Meeting, and in the fall of 1799 was appointed a representative. Her Sunday school for children increased rapidly, and here she began to show her remarkable power over audiences. She paid great attention to the manner of reading (for she objected to the way the Bible was usually read), and it must have been here that she began to develop the very remarkable style that was so effective throughout her life.

She was married when just 20 to Joseph Fry, the son of another prominent Quaker family. The Frys were also well-to-do and were in business in London. Unlike the Gurneys, they were the strictest of plain Friends. You well imagine that this important step was not taken without due deliberation. Elizabeth felt that she had a distinct work, and like so many young women of to-day she was loath to give it up. The sisters helped in the decision by filling their diaries with hopes and prayers that Betsy might make no mistake. Joseph Fry's first proposal was refused, but thinking from the tone of a note that he might receive a different answer, he went back to Earlham. Augustus Hare, from whom I quote, gives a most amusing account of the outcome. Joseph Fry did not dare risk a second proposal so "he bought a very handsome gold watch and chain and laid them upon a white seat. . . . 'If Betsy take up that watch,' he said, 'it is a sign that she accepts me, but if she does not take it up by a particular hour, it will show that I must leave Earlham.' The six sisters concealed themselves in six laurel bushes, in different parts of the grounds, to watch." When Betsy first discovered the watch she retreated to the house, but the sisters kept up their vigil from the laurel bushes. Just where Joseph Fry was the account does not state, but continues: "Once again did the anxious sisters see Betsy emerge from the house, with more faltering steps this time, but still inwardly praying, and slowly, tremblingly, they saw her take up the watch, and the deed was done."

Upon going to London Elizabeth Fry was thrown into quite new surroundings, and it is amusing to find that, although she was considered austere and plain among the Gurneys, among the Frys she was looked upon as far too gay and too much given to worldly customs. Her children came rapidly, and by a most unusual circumstance in exactly the number and order as to sex as her mother's, and as each one came it was given the name of the corresponding Gurney child. Her health was not good, and these first years were largely taken up in adapting herself to her new surroundings. She was always helping those in want when they came to her attention, but took no special part in public charities.

An interesting incident occurred shortly after her first child was born, and we find in her journal (*A Memoir of the life of Elizabeth Fry, 1847, Vol. I, p. 108*) the following:

Mildred's Court, Eleventh Month, 25th (1801). My cough has been so poorly that my husband called in Dr. Simms. I asked his advice about our little one being inoculated; he strongly recommended the cow-pox, and said that he would undertake the care of her if we liked: I think highly of his judgment, and I believe it to be our duty to avoid evil, both bodily and mentally. So trifling a complaint as the cow-pox, being likely to prevent so dreadful a disease as the small-pox, at least it appears justifiable to try it; although the idea is not pleasant, it almost looks like taking too much on ourselves to give a child a disease. But I altogether was easy to do it. I felt a good deal about the operation, which was very little and easily performed. What a wonderful discovery it is if it really prevents the small-pox.

You may remember that the first vaccination with cow-pox was done by Jenner in 1796, just six years before this incident.

She became an ardent advocate of vaccination, and when, after the death of her father-in-law, in 1811, she moved to the large country place at Plashet, in the parish of East Ham, she herself vaccinated the children of the parish, having been taught the method by Dr. Willan, an early and earnest exponent of the practice. She inspected the children from time to time to see that none were left unvaccinated. In these villages small-pox became practically extinct.

Elizabeth Fry soon became the philanthropic Lady Bountiful of the parish, and there was nothing for the good of the people that she was not busy about. She saw that the sick and injured were visited, established a depot for the distribution of clothing, and in winter she had soup prepared at her house in such quantities as to supply hundreds. With the help of the clergyman and his wife she established a school in which 70 girls were taught.

From the first, after moving to London, Elizabeth Fry was active in the Society of Friends. She spoke more and more frequently in Meeting, and in 1811 her gift was formally acknowledged by the Meeting and she became a recommended minister.

The Frys entertained Friends constantly, and it was not often that they did not have one of Elizabeth Fry's brothers or sisters from Earlham staying with them. After moving to Plashet the household became still more complicated, and there are many notes in her journal telling of the thought that she gave to her household, particularly to the proper treatment of servants.

Her first 10 children were born in 16 years, and the last child six years afterwards, November 1, 1822.

In 1813 she paid her first visit to Newgate Prison where she was much impressed by the misery of the women. There is nothing in her journal, however, that suggests that at that time she felt prison reform to be her great work, and it was not until three years later that she made her second visit, this time at the instigation of two of her brothers-in-law. The condition of this prison was most lamentable and some of the descriptions are hard to believe. Years before John

Howard had called attention to the prisons in England and had had laws passed by Parliament for their betterment, but these laws seem to have been at this time almost completely disregarded. The part of Newgate in which the women were confined was the worst part, and the conditions were those of utter squalor, misery and vice; indeed, they were so terrible that the governor himself went there as rarely as possible, and it had for one of its titles "Hell above ground." All the women were herded together without any attempt at classification. There were many children among them, filthy and half-naked. It was in these discouraging surroundings that Elizabeth Fry and her companion requested to be left alone with the women. I doubt whether upon going there she had any plan formed in her mind, but with her quick instinct she made the one appeal that was most likely to be effective. She spoke to the women of their children and showed them how their behavior was affecting them, and she suggested that, if they would co-operate with her, she would form a class to instruct the children, but that this must be with their co-operation and that they themselves were to select one of their number to be the teacher. The women immediately grasped at the plan and by the next visit they had chosen Mary Connor, a young prostitute convicted for stealing a watch, to be the school-mistress.

It was in these discouraging circumstances that the work began. The prison authorities were entirely skeptical as to the outcome, but allowed Elizabeth Fry and her associates to try it. The plan succeeded from the first and it was not long before numbers of the older women were clamoring to be allowed to attend the classes. Other ladies joined Elizabeth Fry and visited the prison daily, and it then became possible to extend the work to the older women. The women were divided into different groups, a monitor from among their number was chosen for each group, and occupation was provided for them as well as daily Bible readings and other instruction. A matron over the women prisoners was also introduced.

To do all this required a considerable sum of money which was provided by the committee, especially by Elizabeth Fry and her brothers. The visiting committee of ladies became later the British Ladies' Society for Promoting the Reformation of Female Prisoners, with many branches throughout the kingdom.

The changes that followed these reforms on the women's side at Newgate were so marked and occurred so quickly that they attracted widespread attention, and two years after their inception, in 1818, Elizabeth Fry and her brother, Joseph John Gurney, visited many of the prisons in Scotland and the north of England. The notes (*Notes on a Visit Made to Some of the Prisons in Scotland and the North of England in Company with Elizabeth Fry, etc., London, 1819*) of this visit were published by Mr. Gurney. The state of each prison they visited is recorded and at the end of the book he has brought together their ideas as to prison management. Later, Eliza-

beth Fry published her views on this subject (*Observations on the Visiting, Superintendence, and Government of Female Prisoners, London, 1827*), and they can also be learned from the reports of various Parliamentary Commissions before which she gave testimony. In brief, she believed it essential that the women prisoners should be entirely separate from the men prisoners, that they should be under the direct care of only women, and should be visited by the men officers only in the presence of women; that the women prisoners should be classified, the tried from the untried, the more hardened offenders from those less so, etc.; that they should be properly clothed, fed and warmed; that the uniform of each class should be different, and that prisoners should be graded according to behavior. She insisted upon the importance of instruction, particularly religious, and urged that the Bible be read to them daily and that it should always be within easy access. Useful occupation she regarded as of first importance, the occupation being so planned as to bring them some remuneration while in prison and to help them to earn their living when they were released. She did not feel that the lot of the prisoners should be made too easy, but she insisted that the first idea must be that of reformation. Solitary confinement she believed to be open to grave dangers, although she advocated strongly that each prisoner be alone at night. She earnestly opposed capital punishment in general, and especially when it was administered for trifling offences as it was at that time.

The importance of the supervision of prisoners upon their release was also insisted upon, and the ladies of the committee gave special attention to those women who were to be transported to the penal colonies in Australia. The condition of these women had been most deplorable and their residence in the colony a scandal. The committee was instrumental in providing work for the women to do during the voyage, matrons to have charge of them and proper methods for their reception and care upon arrival.

Elizabeth Fry had the great satisfaction of seeing practically all of her suggestions adopted, and it was not long after she had begun her work for the prisoners that to her consternation she found herself famous. Few distinguished people visited London without accompanying her to her class at Newgate. Her advice was asked by very many people; she appeared before committees of Parliament and many Societies. Her influence was little short of marvellous. Correspondence was established with philanthropic persons in various countries in Europe. She gave advice as to the management of prisons and the care of the insane. She had long correspondence with the philanthropic Venning brothers, John and Walter, who were living in St. Petersburg. It was through them that she sent advice as to the improvement of the lunatic asylum at St. Petersburg, in which the Dowager Empress had become interested and which she had taken under her special care. Elizabeth Fry recommended cast-iron window frames instead of the clumsy iron bars which had been used in the old institution. She also recommended that all except the

violent lunatics dine together at a table covered with a cloth and furnished with plates and spoons. Here, as everywhere, she felt the importance of the Bible, and the New Testament was introduced into this institution.

To show how closely Elizabeth Fry's suggestions were followed, I shall quote portions of a letter from Mr. Venning written after her death (Memoir, Vol. 1, p. 387):

When I received a letter from your mother I always wrote it out in French and presented it in that language to the Empress, and when she had read it, it was very encouraging to see with what alacrity she ordered one of her secretaries to translate it into Russian, and then deliver it to me to be conveyed to the asylum, and entered into the journal there for immediate adoption. I remember, on one occasion, taking a list of rules, at least 14 in number, and the same day they were confirmed by the Empress; and these rules introduced the following important arrangements, viz.: The treating the inmates, as far as possible, as sane persons, both in conversation and manners towards them—to allow them as much liberty as possible—to engage them daily to take exercise in the open air—to allow them to wear their own clothes, and no uniform prison dress—also to break up the inhuman system of permitting the promiscuous idle curiosity of the public, so that no one was allowed to see them without permission; a room on entering the asylum was prepared for one at a time, on certain days to see their relations. The old cruel system drew forth many angry expressions from the poor lunatics, "Are we wild beasts to be gazed at?" . . . Another important rule of your mother's was, most strictly to fulfil whatever you promise to any of the inmates, and above all, to exercise patience, gentleness, kindness and love towards them; therefor, to be exceedingly careful as to the character of the keepers you appoint. These are some of the pleasing results of your mother's work. The Dowager Empress on one occasion, conversing about your mother, said, "How much I should like to see that excellent woman, Madame Fry, in Russia."

Her health was never very strong, but even when ill she could not restrain herself from trying to put right what she thought was wrong. On one occasion, in 1824, when resting at Brighton, she noticed the great number of beggars and how the charity was given indiscriminately, and seemed to be doing more harm than good. To meet this she organized the charitably disposed among the different religious denominations into the "Brighton District Society," which was, in effect, a charity organization society, and, so far as I know, the first one ever formed. After this she was instrumental in establishing similar ones in many other places.

It was during this stay at Brighton, while she was suffering from frequent attacks of faintness at night, for the relief of which she was often taken to the window of her room overlooking the sea, that her sympathy was aroused by the constant sight of the blockade man, or coast-guard, pacing the beach. She thought how lonely and isolated his life was and wondered how she could help him. She took the first opportunity of speaking to one of these men, but discovered that it was against orders for the men to speak to any stranger, as their duty was to prevent smuggling. To protect the man she gave him her card with the request that he give it to his superior officer. Some days later she was much pleased to receive a visit from the naval lieutenant in charge of the sta-

tion and he explained to her the nature of the service. Mrs. Fry with her clear insight at once thought of a plan, probably the best, that might alleviate the hard lot of the coast-guards—she established libraries containing the Bible and other books. The libraries became very popular and were distributed throughout England. Another national society was formed to look after the interest of this work. Official sanction was given and certain grants allowed. The report of the committee in 1836 shows the magnitude to which the work had grown. This report ends as follows (Memoir, Vol. II, p. 229):

The means thus so liberally afforded, have enabled the committee to provide and forward to the coast,

193 libraries for the stations on shore, containing . . . 25,896 vols.

74 libraries for the districts on shore, containing . . . 12,880

43 libraries for the cruisers, containing . . . 1,867

School books for the children of the crews of

stations . . . 6,464

Pamphlets, tracts, etc. 5,357 in No.

Making a total of 52,464 vols.

and thereby to afford a body of deserving and useful men and their wives and families (amounting to upwards of 21,000 persons) with the means of moral and religious instruction, as well as profitable amusement, most of whom, from their station in life, have not the means of procuring such benefits from their own resources, and who, in many instances, are so far removed from places of public worship and schools, as to prevent the possibility of themselves or their families deriving advantage from either.

Mrs. Fry's interest in public institutions spread over the whole of England, Scotland and Ireland, and many branches of the British Ladies' Society were started in all of these countries. In 1835 she extended her influence to the Channel Islands and visited them again in the following year. The acts of Parliament pertaining to prisons did not apply to these islands, and their prisons were in a lamentable state. As usual, she was able to suggest many improvements in their management that could be and were carried out. Many of her correspondents urged her to visit the Continent and give them the aid of her experience and personality. She felt it her duty to comply with this call, and in 1838 she began her "Visits of Gospel Love" to Europe. She made five such visits, and, as Friends would say, the way was wonderfully opened for her. Those in authority were nearly all more than anxious to have her visit their institutions to suggest improvements. The various royal families received her most cordially and appeared to delight in her society. She must have made a picturesque figure in such surroundings, dressed as she was in the simple elegance of the plain Friend which harmonized so perfectly with her erect carriage, her dignified bearing and her earnest, sympathetic face. Her principles did not allow her to do many of the things that were considered necessary in court, but this seems to have made no difference. Royalty in general seemed more pleased that she advised them and prayed with them than if she had kissed their hands. She suggested many things about the conduct of their prisons, asylums and hospitals, told them of her views as to the

religious state of their kingdoms, and when there was religious persecution—as was frequently the case—she pleaded for religious freedom. All this she was able to do with such wisdom and tact that her counsel was accepted in the spirit in which it was given and very frequently was acted upon.

She visited the Prussian Court twice, in 1840, where she was received with peculiar consideration, and when the King of Prussia, Frederick William IV, visited England in 1842, to stand sponsor for the Prince of Wales (the late King Edward VII), he insisted, somewhat to the consternation of those who had charge of his entertainment, in spending much of his time with Elizabeth Fry. He requested that she dine with him at the Mansion House, went with her to visit Newgate Prison, and then took dinner with her and her family. He was heard to say, "She is the best friend I have in the world."

Little did Betsy Gurney think when she renounced the pomps and follies of the world and adopted the customs of plain Quakers, that the path she had chosen was to lead her so often to the seats of the mighty!

Although Elizabeth Fry saw many things to criticize in her journeys to Europe, she also found things to commend and she met with many earnest workers for the amelioration of the distressed. It was during her first visit to Germany that she visited Pastor Fliedner's establishment at Kaiserwerth—an establishment for the training of nurses, the first secular one that had ever been established. Fliedner had corresponded with Mrs. Fry, had visited her on two occasions and seems to have been much influenced by her example. Mrs. Fry, on her part, upon returning to England followed his example and established the first band of professional nurses in Great Britain. She herself could not take a very active part in it, but her sister, Mrs. Samuel Gurney, and some other ladies took the management of it. When not engaged in nursing, the "Nursing Sisters" resided at "The Home," in the city. They wore a plain but inconspicuous dress and were maintained and paid by the institution, but were not permitted to receive any money or gifts under any circumstances for their attendance in illness. The funds of the Society were small and were derived partly from subscriptions and partly from the liberality of those who were benefited.

The intimacy between Elizabeth Fry and the other members of the Earham family never waned and she paid frequent visits to Norfolk. Her sisters for the most part differed from her in religious matters, but this difference was never allowed to cause any break between them. Whenever there was illness, Elizabeth Fry, when possible, nursed the sufferer in a peculiarly sympathetic, skillful manner. However strict she may have been with herself, she was more than lenient with everyone else and had a never-failing sympathy. This to some extent must have been due to the fact that she herself suffered frequently from bodily ills, particularly those most troublesome ones of a nervous nature, and she had a most unusual insight into such troubles.

In the Memoir² her daughters have included in the extracts from her journal a number of notes which bear on her bodily state. These give some idea how, in her case, a peculiarly nervous, sensitive nature was controlled and directed and made most wonderfully effective by a firm religious belief. These extracts are probably only a few of many similar ones to be found in the original journal, but they are, I am afraid, too many to be included in this paper, and so I have been forced to select some which seem most interesting. I have already read you her own recollection of her childhood in which she speaks of her childish fears and nervousness. When she was 18, during her religious awakening, she shows in the following extract how she was struggling against her morbid fears:

Jan. 4, 1799. A plan, at least a duty, that I have felt for some time, I will now mention. I have been trying to overcome fear; my method has been to stay in the dark, and at night to go into those rooms not generally inhabited; there is a strange propensity in the human mind to fear in the dark, there is a sort of dread of something supernatural: I tried to overcome that, by considering as far as I believed in ghosts, so far I must believe in a state after death, and it must confirm my belief in the Spirit of God; therefore if I try to act right, I have no need to fear the directions of Infinite Wisdom; I do not turn away such things as some do. I believe nothing impossible to God, and He may have used spirits as agents for purposes beyond our conceptions; I know they can only come when He pleases, therefore we need not fear them. But my most predominant fear is that of thieves; and I find that still more difficult to overcome, but faith would cure that also, for God can equally protect us from man as from spirit.

Before and after the birth of each child she usually suffered a period of depression, accompanied by great bodily weakness and a terrifying apprehension of death. After the birth of her second child, when 23, she writes:

Plasnet, Fifth Month, 21st, 1803. I have long been prevented writing in my journal, by a severe attack of indisposition. It is difficult exactly to express what I have gone through, but it has been now and then a time of close trial; my feelings being such at times as to be doubtful as to whether life or death would be my portion. One night I was, I believe, very seriously ill; I never remember feeling so forcibly how hard a trial it was in prospect to part with life. Much as my mind, as well as body, was then tried in this emergency, still I felt forcibly an inward support, and it reminded me of that text of Scripture, "Can a woman forget her sucking child, yea they may forget; yet will I not forget thee." And then I told those around me, that I was so ill, I could almost forget my child, but I felt the existence of a power that could never forget. I have gone through much since, in various ways, from real bodily weakness, and also the trials of a nervous imagination: no one knows but those who have felt them, how hard they are to bear, for they lead the mind to look for trouble, and it requires much exertion not to be led away by them; nothing I believe allays them so much as the quieting influence of religion, and that leads us to endeavor after quietness under them, not looking beyond the present. But they are a regular bodily disorder, that I believe no mental

² Memoir of the Life of Elizabeth Fry. Edited by two of her daughters. London, 1847.

exertion can cure or overcome, but we must endeavor not to give way to them.

Again six years later she records:

Seventh Month, 27th, 1809. I am much better than I was, but I have believed, in these trying complaints to which I am liable, that the less I look outwardly for help the better; as I do not believe any doctor can do much for me. I feel the best satisfied when I simply endeavor to bear them patiently; I think I know myself, what is the best to take for them: they appear to be principally nervous, which I consider to be beyond the power of man either to understand or cure; but how often have I experienced true spiritual support and help, when I have endeavored patiently to wait on the source of good: and the mind being so nearly connected with the body, whatever tends to tranquillize it, really helps the complaint.

She often was pursued by the thought that possibly her nervous depression might be due to a lack of faith, and an evidence that she was in some way untrue to her religious standards, although her intelligence told her that the condition was largely a physical one as is shown by the following extract:

Plasnet, Fourth Month, 30th, 1814. None know but those who suffer from them the deep humiliations such disorders create, as those I have lately had; I mean great bodily weakness, accompanied by nervous lowness of spirits, and much mental fear. In the first place, how deeply do they try us, being in their own nature so painful; in the next, from the difficulty in doing strictly right in them, how far to endeavor to divert by cheerful amusement, or by taking such things as may soonest relieve them; and added to these, I think many are apt falsely to accuse themselves, and to mistake the painful restlessness and fear occasioned by them, for impatience and mistrust; I have sometimes a hope that this is not my case, though at others great fear arises, lest I should in any degree let go my hold, or be impatient after having so abundantly known the goodness, the loving-kindness of the Almighty. Oh, saith my soul, may He once more revive the spirit of His poor unworthy one, and breathe upon these dead bones, that they may live.

The neurotic disposition seems to have been an inherited tendency in this remarkable family, and Elizabeth Fry, when 53, wrote to one of her daughters, who was evidently suffering, the following helpful and encouraging letter:

(1833.) I feel in the first place, earnestly desirous that thou shouldst think as little as possible of thy nervous feelings. I know how extremely painful they are, but experience has taught me, the less I think of them the better. It is most important to look upon them as much as possible like the toothache—that it must be endured while it lasts, but it is not dangerous in its nature. As for the discolored view, the imagination may at times give to things, nothing is more important than to set it down as a clear and fixed thing in the mind, that whilst this nervousness lasts it is not sound, and must not be believed or taken heed to. I would not have thee discouraged at this return of it. I believe I never had death brought home very closely, without being brought into a low nervous state, it is after all so awful; though I increasingly see, that this is real weakness, and that those who are believers in the Lord Jesus, however unworthy, need not fear it, as through Him its plague and sting will be done away. But it is folly in one sense to look ahead, we have enough to do to seek for help and grace for the present time to do our present day's work. When the day comes that we have to give up "this mortal life," we may and ought humbly to trust,

that through the unmerited mercy and love of our Lord, His grace will be found sufficient for us. I observe, for my great encouragement, that what we call nervousness often proves no common blessing, if made a right use of, and not given way to. It so wonderfully humbles, prevents the creature glorying, and makes willing to do anything to come to that peace, which quiets every storm. Thy uncles and aunts have nearly all been striking instances of this: and I believe, hard, very hard as it is to bear, it is a baptism to fit for a fulness of joy and glory rarely partaken of; but it in no common degree calls for patience. I always think both David and Paul largely partook of this sort of humbling experience. Therefore my dear . . . if tried this way, possess thy soul in patience, and look upon it as a suitable, though bitter, medicine prescribed by the Physician of value to promote thy health and cure.

She always, while engaged in her various philanthropic activities expended her strength most lavishly, and afterwards she usually had periods, often long ones, of great suffering. Together with the physical weakness, the accompanying mental depression was often combined with the fear that she had received far too much personal adulation, and that she had perhaps put herself forward unduly. She was glad to use the power of her reputation and position in the furtherance of her projects, but was very fearful that she might take to herself—the instrument—the credit that was due to her Lord, and she at times looked upon her illnesses as corrective agencies.

As she was returning from her second visit to Germany, when 61, she writes, in a letter to her husband and children, the following:

Cassel, Ninth Month, 26th, 1841. I have continued very far from well, with latterly a considerable stiffness in my limbs, so that I am obliged to be assisted to walk upstairs, and helped into the carriage, sometimes by one or two men. I might have had the same attack at home; but one thing is certain, we may fully trust in our Heavenly Father, who is constantly protecting us under the wing of His love, and who knows what is best for us. I have sometimes thought that after being so helped on my way, from the palace to the prison, it was likely that the poor instruments should need a little further refining and purifying, for our works are to be tried as by fire. I have very earnestly desired not to repine, or to be unwilling to drink the cup that may be given me to drink. We travel with six horses to make the greatest speed home. I have a board in the carriage, that when your uncle and Anna are outside, I can quite rest and make a real sofa of it, when I need it, which I do for one or two stages in the day. Mary and François are very attentive and kind; indeed how differently am I cared for to many poor missionaries. I wish you to feel for me, but not to be too anxious about me; commit me entirely to Him who only knows what is best for me. Your mother's Philadelphia letter was very seasonable and acceptable. I wish her and all my children to know how it is with me, for I need their sympathy and prayers, at the same time that I feel the best help to be near, and the Power that says to the waves "So far shall ye go and no further." Often in my wakeful and at times distressing nights, a sweet peace comes over me to calm my troubled spirit. We hear from newspapers, that the poor Baptists in Copenhagen are to be released from prison, a small sum being paid by way of fine. What a comfort! and the poor Lutherans in Prussia say they are now so well off, that they do not wish us to ask for any more liberty for them from the King.

After this visit Mrs. Fry's health improved but slowly and, although far from well, she felt it her duty to go again to

France in 1843. Upon returning from this visit her health failed rapidly and she was practically an invalid from then until her death, although she was able to continue her correspondence and at times to take part in the various national societies she had founded.

Among the number of interesting references in the Memoir to this time I can only include the following:

One afternoon, when one or two members of her family were reading to her, she was unable to attend to a very interesting religious biography, saying, it was too touching to her—too affecting. She added, after a pause, "How I feel for the poor when very ill, in a state like my own, for instance, when 'good' ladies go to see them. 'Religious truths so strongly brought forward, often injudiciously.'"

As she became weaker her fear of death decreased and to one of the "Nursing Sisters" she thus expressed herself, "I am of the same mind as Paul, I can say, 'to me to live is Christ, but to die is gain.'"

Shortly before her death her daughters record a marked change in her dominant disposition:

There was another wonderful change. Her powerful understanding and great capacity had given her the habit of control—she was accustomed to power. During her long illness, this continued more or less to show itself, and it was not always easy to distinguish how far her opinions about her own treatment and capabilities were well founded or not. This feature of her character had disappeared. The will seemed wholly broken, the inclination to resist, or even strongly to desire anything, passed away; and she was content to leave little things and great to the direction of others. It was inexpressibly affecting to see her look of meek submission, to hear her plaintive answer, "Just as you like," to those about her.

These extracts that I have read show clearly how much Elizabeth Fry suffered throughout her life from her peculiar nervous organization. For two years before her death in 1845 she was an invalid, confined practically to her bed or chair. Exactly what organic trouble she had, I have been unable to determine, for her daughters speak only in very general terms of the symptoms. She became less and less able to take any active part in the various movements she had been instrumental in starting. She, however, attended Meeting whenever possible, often when she was too feeble to leave her wheelchair, and it is said that her mind remained remarkably clear in regard to her ministry, even when she found it very difficult to concentrate her attention on other subjects.

During the last months of her life she appears to have suffered intensely, and her strong will seems to have become passive, but her condition did not become acutely alarming until three days before her death when, I think, she must have had a thrombosis of the cerebral blood vessels. She gradually became unconscious and died October 12, 1845.

Elizabeth Fry's religious faith never wavered, nor did she ever regret having become a plain Quaker. She suffered

much for her principles, particularly from the fact that many of her sisters and brothers could not see as she did and that most of her children separated themselves from the Society. Her eldest son renounced his membership and others were disowned for marrying out of Meeting. She believed most strongly that young people should be left free in their choice in marriage and encouraged her children in this by her sympathy and love. She felt as a minister of the Society of Friends that she could not go to their weddings, but she did attend the Meetings in which their names were taken from the list of members.

She was thrown much with earnest people of all denominations and had no trouble in uniting with them all. Her attitude to others was one of love and helpfulness, but of herself she was a severe critic. Although she felt it right for herself to conform rigidly to the customs of Friends, she regarded it as a personal matter, and saw clearly that such conformity might be a stumbling block to others, particularly to the young. She had little patience with the empty forms of piety, whether in plain Quaker or in the most ritualistic of priests. Her religion was one of service and she truly followed George Fox's injunction, "That which Friends do speak they must live in."

Augustus Hare (Gurneys of Earham, Vol. II, p. 201) writes of her wonderful tenderness:

Mrs. Fry used pathetically to say at this time that she had been "undermined by excessive love," an expression touchingly significant of the secret spell of Elizabeth Fry—the spell which unlocked the hearts of kings to her, and caused the prisoners' chains to fall off at her approach. She had been no professional philanthropist, too much absorbed in humanity at large to care for the human item, but the public work had been, as it were, only the overflow of her woman's heart, the expression of the fullness that remained after children, grandchildren, brothers, friends, had been loved with an intensity which to her eyes seemed "excessive," almost sinful. This marvellous tenderness it was, thrilling in the tones of a voice whose natural music would have been almost sufficient to melt and convince, which had been the key to her influence and power—this, and her sweet humility of soul, her child-like, single-eyed devotedness.

This certainly accounts for the charm and appeal of her personality, but her effectiveness was due, I think, to the fact that she had a most remarkable faculty of grasping a situation and knowing, seemingly intuitively, what under the circumstances should be done to meet it. This is genius, and when genius is activated by Christian love what may it not do and who of us would not gladly follow?

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DEGENERATION GRANULES AND VACUOLES IN THE FIBROBLASTS OF CHICK EMBRYOS CULTIVATED *IN VITRO*

By WARREN H. LEWIS

(From the Department of Anatomy, The Johns Hopkins Medical School)

INTRODUCTION

The formation of granules and of fluid vacuoles within the fibroblasts of tissue cultures is of frequent occurrence in plasma and in Locke's solution, with or without the addition of other substances. There are other types of degeneration. This vacuolation of the cytoplasm is one of the more common modes of cell degeneration and death in tissue cultures. It has, however, received but little consideration, partly because the vacuoles have often been confused with fat droplets and partly because investigators have been reaching out in other directions.

Lewis and Lewis (15) considered somewhat briefly the granules and vacuoles appearing in the cells of culture, especially the granules which stain with neutral red, Nile blue B extra, and brilliant cresyl blue 2b. In the normal cell the granules were few in number, but were plentiful in cells with many vacuoles. It was also noted that they accumulate about the central body (centrosphere) and are similar to the granules within the vacuoles. No relationship was found between these granules and mitochondria.

The authors also dealt somewhat briefly with the vacuoles found in the cytoplasm, recognizing that they were signs of degeneration of the cytoplasm and that there was a progressive accumulation in some types of degeneration until most of the cytoplasm was used up and only a framework remained. At first it was somewhat difficult to distinguish the vacuoles from the fat globule spaces in fixed and stained preparations, but in the living cells no such difficulty was encountered. Small dancing granules, varying in number from one to many, were seen within the vacuole; sometimes the granules were motionless and adherent to the wall of the vacuole. It was also found that at times they were colored pale green with janus green. With Nile blue B extra and brilliant cresyl blue 2b the contents of the vacuoles stained pink, and the granules blue or purple. Changes in the shape of the vacuoles and the formation of very unstable, thread-like processes extending out from them were also observed. We were unable to trace any relation between mitochondria and vacuoles, although it was often noted that the mitochondria changed from threads and rods to granules and vacuoles, and that the contents of the

number of granules and vacuoles, and that in extreme vacuolization the mitochondria were lodged in the cytoplasmic framework between the vacuoles.

Maximow ('16) noted in plasma cultures of subcutaneous tissue of the adult rabbit, fixed with Zenker-formol, embedded in celloidin, cut into histological sections, and stained with cosin-azur, that the fibroblasts contain singular granules which stain bright pink—i. e., are slightly acidophilic. At first these are minute and irregularly scattered in the cell body in small groups. The number of granules varies, but increases with the age of the culture. "In old cultures without cell proliferation all fibroblasts are often crowded full, up to the very end of their outgrowth, with large, round, closely packed granules. . . . Besides the above granules the protoplasma of many fibroblasts of the same preparation contains small and large vacuoles." In some vacuoles a large or small acidophilic granule of the same character was occasionally detected. Maximow states that the impression produced is that the granules dissolve from the outside inward and form the vacuoles, and that the granules become permanent constituents which are transmitted to subsequent cell generations. He further finds that "the whole cell-body and its processes are then crowded full of spherical, occasionally very large, granules, so that but little is seen of the protoplasm itself." He regards this as an adaptation for life outside the organism. The vacuoles usually present are either scattered singly or joined in groups. "In the fibroblasts embedded in the masses of the old fibrin the majority of the large granules are substituted by vacuoles and the structure of the cell-body appears therefore coarsely foamy." These granules and vacuoles found by Maximow in the fixed and stained cultures of the subcutaneous tissue of the adult rabbit correspond to the granules and vacuoles previously described by Lewis and Lewis, and are probably similar to the ones considered more in detail in the present paper.

Maximow concludes, from cultures fixed in Zenker-formol and stained with iron hematoxylin after sectioning, that the above-described acidophilic granules represent the product of the direct transformation of the chondriosomes. He bases this view upon the very distinct pictures secured by the above method. He says: "The black chondrioconts change into round granules—the mitochondria, which increasing in size seem to transform themselves into the acidophilic granules." This theory regarding the derivation of the above-considered granules and vacuoles from mitochondria is probably quite incorrect. The two types of cytoplasmic inclusions have nothing to do with each other. Maximow's conclusions are such as might be expected from the methods employed by him. He introduces the article under consideration by the statement that heretofore tissue-culture has lacked exact, authentic, systematic researches of a histological character, and that "we lack till now precise information concerning their microscopic structure, their correlation, and, above all, their origin from determined, well-known elements of normal tissue." After this introduction he proceeds to show how cultures should be studied. What could be more absurd than

to base practically all conclusions upon observations made on tissue-cultures that have not only been cut into sections, but have also been fixed in the same old mixtures that have so often led observers astray in normal tissues. The very thing we are trying not to do in tissue-cultures is what Maximow seeks to introduce with his histological technique. The absurdity of depending almost entirely upon histological technique, section cutting, etc., will, I think, be obvious to most American observers familiar with cultures. The greatest value of the tissue-culture method lies in the fact that it admits of a study of the living cell, and affords an opportunity actually to watch some of the changes which take place therein, both under the usual conditions of the culture and under various experimental conditions through the introduction of known factors, such as vital stains, various chemical substances, drugs, poisons and other alterations of the medium. Maximow gives little or no attention to observations on the living cell, at least as far as one can judge from his article. This is partly due, no doubt, to the fact that living cells are not so easily observed in plasma as in fluid media. I do not wish to undervalue the use of fixed and stained material, especially total mounts (we use them extensively); but the pictures found in fixed and stained material should be interpreted and controlled from extensive observations upon the living cells. The emphasis, in fact, should be laid on the study of the living cells, and this we have constantly done. It is, of course, more easily accomplished when fluid media are used and the culture grows out on the under surface of the cover-slip, than with the use of plasma. The fixed specimens are of great help in the construction of illustrations, and some structures are more clearly revealed than in the living; but unless they are to be seen also in the latter, their existence in the living cell, as seen in the fixed specimen, must always be open to question.

Maximow criticizes our methods very severely: "In view of the imperfection of their methods (the preparations were made by vapors of osmic acid and examined *in toto*, without making sections) their results are of but little importance." In the first place, osmic acid vapor, with the virtues of which Maximow is apparently not familiar, is a most excellent fixative for cultures in fluid media, far better than any of those employed by him—we have tested them all. It may not answer as well for plasma cultures, but with that we are not concerned. In the second place, there is little point in making sections of cells that are already flattened out on the cover-slip, unless one wishes to trace their origin from the old piece; for that purpose we have, of course, occasionally made sections.

Maximow also criticizes, as have others, the use of Locke's solution. We have never claimed that this solution alone contained all the necessary food-stuffs, but with the addition of dextrose and bouillon or egg-yolk the need can be partially met. Just how complete a supply of food can be given in this manner has not yet been determined. Cultures have been kept alive for a month by washing and changing the medium every day or two, and possibly they might be carried on much longer. The cultures in plasma degenerate somewhat more slowly, as a rule, than those in our solutions, but here also

replantation is necessary for long continued growth. Burrows and Neymann ('17) believe that food materials for the growing cells, in both isotonic salt solutions and plasma, come directly from tissue fragments in the explanted piece through disintegration caused by unfavorable environment. We have long thought that some of the food elements might be supplied in this manner. The conditions, of course, are not normal either in plasma or in Locke's solution, but the first fibroblasts that grow out into the media show no abnormal cytologic changes. The conditions in these embryonic chick fibroblasts undoubtedly differ somewhat from those found in the adult mammalian fibroblasts studied by Maximow.

Burrows and Neymann find that the cells *in vitro* "come to rest after a short period and show evidences of deterioration through vacuolization and failure to stain deeply." These authors evidently recognize that vacuolization is a sign of degeneration. We have not found that the process interferes with the staining of the cells unless they are dead before fixation. A cell may be almost completely filled with vacuoles and yet stain brilliantly with iron hematoxylin and a counter stain.

Luna ('17) found small vesicles or vacuoles appearing in the pigment cells of the retina, cultivated *in vitro*, and as their number seemed to increase with a corresponding decrease in the mitochondria, he thought it probable that they were derived from the latter. Vesicles such as he pictures in his Fig. 7 correspond to the mitochondrial vesicles already figured and described by us in degenerating cells (1915). They do not correspond to the degeneration vacuoles described in the present paper.

MATERIAL AND METHODS

Most of the observations were made on small explants from the legs of 6-, 7-, and 8-day chick embryos cultivated in the usual manner in Locke's solution plus 0.5 per cent dextrose. Such cultures show fibroblasts, clasmatoocytes, and often ectodermal membranes and muscle-buds. The cultures of this special series usually reached the maximum growth in about 48 hours. Some of them showed more or less degeneration at 72 hours, and at 96 hours most of the cells were completely degenerated and dead.

I wish to emphasize here that the particular series of cultures (several hundred) used for these observations were made by an inexperienced assistant and that the number of cultures showing granular and vacuolar degeneration was far in excess of that shown in any of our other series where such a mode of degeneration is not by any means the rule. Not only did most of the cultures show such degeneration, but the growth was usually below the average and sometimes there was no growth. I have not been able to analyze the factors responsible for this excessive amount of granular and vacuolar degeneration. The process is, however, essentially the same as that observed in other series except that in the latter case the cultures lived longer with normal appearing cells before degeneration began and that this particular type of degeneration was not so common.

The cessation of growth, of mitotic division, and degenerative changes, may depend not so much on the exhaustion of the food supply as upon the accumulation of waste products in the medium. There was very little fluid in the small drops used in these cultures, and it is possible that it did not take very long for the accumulated waste products to exert injurious effects upon the cells.

Mitotic figures were found in some of these cultures, often many in the same culture at the same time. Such dividing cells are found in the 24-, 48-, and 72-hour cultures. On the other hand, some cultures do not contain a single mitotic figure, and these are usually the ones which show degeneration changes, some even as early as the second day. We are still puzzled by the great differences in the vitality of the cultures, due, perhaps, to unknown factors during the manipulations. This is more especially true when the method is used by an inexperienced worker. The rate and extent of growth are often equal to that seen in plasma.

The living fibroblasts were observed over varying lengths of time in cultures of various ages, both with and without the use of vital stains and various other substances. The vital stains most frequently employed were neutral red and janus black No. 2. The combination of these two stains proved the most satisfactory of all. We have, in the past, frequently used the combination of two vital stains, more especially neutral red and janus green. The latter combination has been used also by Coghill ('15) on fresh amphibian material, and by Mrs. Lewis ('17) on certain eggs and embryos. The neutral red is rapidly taken up by the vacuoles and certain granules of the fibroblasts, while the janus black No. 2 stains only the mitochondria a deep blue-black. Neutral red was used in strengths varying from 1-5000 to 1-800,000 in Locke's solution. For most of the observations I use 1-20,000 or 25,000. The janus black No. 2 was usually of the strength of 1 part of janus black No. 2 to 10,000 or 20,000 parts of Locke's solution. Brilliant cresyl blue 2b and methylene blue (Ehrlich rect. or Harmer Lab.) were also used. These stain the same granules and vacuoles that take up the neutral red.

Until recently we continued to use osmic acid vapor as a fixative with excellent results. Lately, however, the osmic acid in the market has not given satisfaction, and we therefore substituted Zenker's solution without the glacial acetic acid (2.5 per cent bichromic acid solution plus 5 per cent corrosive sublimate plus 1 per cent sulphate of sodium). This has given most excellent preparations when followed, as were the osmic acid specimens, with the iron hematoxylin stain. The cover-slip with the attached growth is immersed in the bichromate corrosive sublimate mixture from $\frac{1}{2}$ to 12 hours, washed and carried through the alcohols with a little Lugol's solution. It must be borne in mind that the procedure here used is suitable for cultures grown in Locke's solution and not necessarily for plasma cultures where the clot acts as a buffer through which the fixatives must penetrate. In cultures in Locke's solution the naked cells are exposed to the action of the fixative and the process is correspondingly rapid, reducing post-mortem changes to a minimum. Comparatively few

cultures were fixed, as we relied upon living material for our conclusions. With the iron hematoxylin stain it was often impossible to distinguish between small granular mitochondria and the degeneration granules, as both are stained black. The study of the living culture aids in the interpretation of the fixed material and *vice versa*. Some points would undoubtedly have been missed if only one method had been employed.

DEGENERATION GRANULES AND VACUOLES

Degeneration granules may be characterized briefly as follows:

- (1) They are rare or non-existent in the more normal, vigorous fibroblasts of the very young cultures.
- (2) They vary in size from the ultramicroscopic granules to ones larger than mitochondrial granules.
- (3) They increase in number with the age of the culture.
- (4) They tend to accumulate about the centriole or centrosphere.
- (5) They are often moved about actively (by cytoplasmic currents), usually in paths from the periphery to the centriole or centrosphere, or *vice versa*.
- (6) They take the neutral red stain with great avidity, also brilliant cresyl blue 2b and methylene blue (Ehrlich).
- (7) They are not stained by janus black No. 2 which stains the mitochondria.
- (8) In fixed specimens stained with iron hematoxylin many of these granules are not distinguishable from mitochondria.
- (9) They do not arise from the mitochondria.
- (10) The degeneration vacuoles develop about them.
- (11) They are probably waste products.
- (12) They accumulate under certain conditions in degenerating fibroblasts, and hence might be called degeneration granules.

The degeneration vacuoles show the following characteristics:

- (1) They are not found in the normal, vigorous fibroblasts of the cultures.
- (2) They are first apparent after there has been a considerable accumulation of granules.
- (3) They always seem to form about the granules and almost always contain one or more granules.
- (4) When first recognizable the vacuoles are small and contain a relatively very large granule.
- (5) They vary much in size.
- (6) They tend to accumulate about the centriole or centrosphere.
- (7) They often move in paths from the periphery to the centriole or centrosphere, or *vice versa*.
- (8) They stain avidly with neutral red, but not as deeply as the granules; they also stain with methylene blue and brilliant cresyl blue 2b.
- (9) They are not stained by janus black No. 2.
- (10) They often change shape in the living cell, all gradations from spheres to long thread-like channels being seen.
- (11) They do not arise from the mitochondria.
- (12) They are probably waste products.

(13) They accumulate under certain conditions in degenerating fibroblasts until the latter are often crowded full of them, and then as the cell dies they disappear and the dead cell has a moth-eaten appearance.

The granules and vacuoles especially considered here are most readily singled out from other cytoplasmic inclusions by their property of rapidly absorbing the neutral red dye. It is well known that neutral red stains certain granules in various types of cells in other animals, and the fact that they absorb neutral red does not necessarily indicate that the granules are identical in composition; very likely they are not. We do not know whether the union of the dye with the granule is a physical or a chemical one. Such granules, however, probably have certain characters in common.

The determination of the presence of such granules in the normal, living embryo or animal is most easily accomplished in small, more or less transparent forms that live in an aqueous environment. In embryos, such as the chick, it is more difficult to ascertain with certainty if such granules are normal in any particular type of cell, such as the fibroblast. The mere act of isolating the fibroblast by separating it from the organism in teased preparations, in spreads, or in cultures, immediately alters the environment. Changes in the normal metabolic activity probably follow immediately, and the formation of such granules may result from the changed environment through alterations in the normal supply of gases, salts, carbohydrates, protein products or through the inadequate elimination of waste products from the immediate environment of the cell.

For the present, at least, we are uncertain whether such granules actually exist in the fibroblasts under the normal conditions of the embryo. Occasionally one finds here and there, in cultures less than 24 hours old, fibroblasts entirely free from granules that take the neutral red stain. If these granules do exist normally they are probably small and few in number. Such fibroblasts exhibit a marked contrast to those found in many of the older cultures.

GRANULES IN THE YOUNG FIBROBLASTS

The healthy vigorous fibroblasts of the young cultures are free from vacuoles and contain very few scattered granules that stain red with the neutral red. In the ordinary cultures there are usually to be found, at the end of 24 hours—in the fibroblasts that have migrated from the explant, or other fibroblasts that have arisen from these by mitosis—scattered, clear, refractive granules. They vary in number, often quite markedly, in different cultures and also in cells of the same culture. After 24 hours none of the fibroblasts are entirely free from such granules and many of them also contain small vacuoles with relatively large granules.

DISTRIBUTION OF GRANULES IN THE HEALTHY FIBROBLASTS

The comparatively few granules seen in the fibroblasts of the very young cultures are scattered through the cytoplasm without any definite arrangement, so far as I have been able to determine. Those in the body of the cell, however, approach

to within varying distances of the edge of the much flattened cells. Granules are not uncommon in the larger processes, and here sometimes, since they may be nearly as large as the diameter of the process, they come close to the surface. It is not surprising that the granules are irregularly and apparently indiscriminately scattered through the cytoplasm, as under the best conditions they often move about, usually in a path from the periphery to the nucleus, or *vice versa*, and are thus constantly changing position. As we shall see later, in the fibroblasts of older cultures the granules and vacuoles come to have a very definite relation to the centriole, and their paths of movement are between the centriole and the periphery, rather than between the nucleus and the periphery. The position of the centriole is difficult to determine until there has been a considerable accumulation of granules, but I think if it could be located in the younger, healthy fibroblasts we should find that the granules were moving in paths between it and the periphery, rather than between the nucleus and the periphery. Its close proximity to the nucleus makes it appear as though it were the nucleus that was the center for such activity.

INCREASE IN THE NUMBER AND SIZE OF THE GRANULES AND VACUOLES

As the cultures get older there is a gradual increase in the number and size of the granules and vacuoles. In spite of great variations in the rate of accumulation and the ultimate size of the granules and vacuoles in different cultures, an accurate picture can be given of the more usual process found in the majority of cultures that undergo vacuolar degeneration.

As the granules increase in number it soon becomes noticeable that part of them accumulate at one side or at one end of the nucleus. In fixed material and in later stages this accumulation at the side of the nucleus is clearly seen to take place about the centriole or centrosphere. It is rarely possible to recognize in the living cell, during the early stages of the accumulation of the granules, the centriole or centrioles at or near the center of the granular mass. Since, however, it is possible to do so in fixed material, and at later stages also in the living cell, I have not the slightest doubt but that this accumulation of granules at one side or at one end of the nucleus always takes place about the centriole. This is a very interesting and important point. It is the centriole, then, and not the nucleus that is most directly concerned in the accumulation or location of degeneration granules and vacuoles.

The centriole or the apparatus surrounding it is the determining factor that in some manner governs, by its peculiar metabolic activity, the accumulation of the granules and vacuoles about it. I shall speak of an accumulation of granules about the centriole in these earlier stages, even though in the great majority of instances the centriole was not positively recognized in the living material.

As the granules and small vacuoles increase in number, then, they accumulate more and more about the centriole. The mass is denser at the center than at the periphery, and there are always a few granules scattered through the cytoplasm. With the increase in number of the granules the presence of small

vacuoles about many of them becomes more apparent. The granules also show more variation in size, in that many of them are larger than before. As the process goes on, the number and size of the vacuoles gradually increase, so that they form an ever-widening halo about the centriole and centrosphere. Most of the granules become enclosed in vacuoles or show more and more distinctly their vacuolar envelope. Vacuolization may continue until the entire cytoplasm is crowded full of vacuoles except for the enlarging centrosphere and a narrow peripheral margin which usually remains more or less clear. The cytoplasm in such highly vacuolized cells is reduced to a thin framework between the vacuoles, and to a clear, well-defined centrosphere about the centriole that is entirely or almost entirely free of granules or vacuoles. Long spindle-shaped fibroblasts, with the nucleus extending nearly the full width of the cell, often have the centriole at one end of the nucleus, and the cytoplasm between the nucleus and that end of the cell may become packed with vacuoles before any appear in the other end of the cell.

The rate of increase in the number of granules and vacuoles varies greatly in different cultures, and also somewhat among the cells of a single culture. There is, however, usually more variation between different cultures than among the cells of the same culture. No two fibroblasts are ever exactly alike, even in the same culture; yet in spite of this dissimilarity among the individual cells there exists enough uniformity to give a peculiar character to each culture. Since the rate of accumulation of the vacuoles and granules varies in different cultures, often quite markedly, one finds occasionally in a 24-hour culture an accumulation of vacuoles and granules as extensive as in the average 48- or even 72-hour culture. On the other hand, it sometimes happens that a 48- or a 72-hour culture presents no greater accumulation of granules than the average 24-hour culture.

There are many other variations in the number, size, inequality of size, etc., of the granules and vacuoles. It is the control and production at will by environmental alterations of such variations that will enable us to analyze more fully the processes that are taking place. It does not seem beyond the realms of possibility that some day we may be able to produce at will any desired variation.

The above conclusions in regard to the increase in the number and size of the vacuoles and granules were not drawn from the continued observations of individual cells over long periods of time, but from shorter observations on thousands of cells in hundreds of cultures. It would probably be possible so to regulate the conditions of observation that one could follow in a single cell this accumulation of granules and vacuoles from the condition found in the healthy fibroblasts, with few scattered granules, to the completely vacuolized cell, and even to the death of the cell.

Often during the observations, through the manipulation of the culture and the application of neutral red and janus black No. 2, the cells were found to live but an hour or so after the observations were begun. Such cells do not exhibit during that hour or two any marked changes in the number or

granules or vacuoles. Their death may ensue at any stage in the granular and vacuolar formation. Death may also take place at any stage in the cultures that are not thus manipulated. Several factors undoubtedly contribute to the death of the cell, and sometimes one and sometimes another may predominate. In the highly vacuolated cells stained with neutral red the final death process is often quite rapid. The behavior of the colored vacuoles is quite striking; one after another, in rapid succession, they suddenly lose their color and flash out of sight. When the process is complete, the cell has a peculiar, clear, unstained, moth-eaten appearance. Changes in the mitochondria and in the nucleus are also to be seen.

SIZE AND SHAPE OF THE GRANULES

The granules vary in size in the same cell. Some are barely visible with the highest powers, even with the neutral red stain; others are of considerable size and may measure one-quarter or one-half the diameter of the nucleolus. The extreme minuteness of some of the granules indicates that other still smaller, ultramicroscopic ones are probably scattered through the cytoplasm. Within certain limits it can be safely stated that the more healthy the cell the fewer and smaller are the granules. The granules undoubtedly increase in size. One cannot actually see this increase, since the process is probably slow and the difficulty of following the same granule through any considerable length of time is too great.

Most of the granules are somewhat angular in outline, suggesting a crystalline formation. There is but a suggestion of this, however, since they are usually irregularly angular. I suppose an irregular angular mass might result from crystallization or from the accumulation of ultramicroscopic particles. Such granules are difficult to distinguish, by their shape alone, in unstained cells, from the small granular mitochondria (when the latter are present). In most healthy cells, however, the mitochondria are in the form of rods and threads which can be easily distinguished from the degeneration granules. In fixed specimens stained with iron hematoxylin it is likewise difficult or impossible to distinguish between granular mitochondria and degeneration granules. There is a method, however, by which the two types of granules can be distinguished in the living cell; *i. e.*, the combination of neutral red and janus black No. 2, by which the granules are stained bright red and the mitochondria blue-black. Some of the special mitochondrial stains also enable one to distinguish the two types of granules in the fixed specimens; on the other hand, certain fixatives, especially those containing acetic acid, destroy the mitochondria, but leave the granules unaffected.

Maximow noted that the granules described by him were at first minute and irregularly scattered in the cytoplasm. This extreme minuteness of some of the granules is an important point, especially in relation to their possible origin from mitochondria, as alleged by some authors; for it would be logical to assume, if they do arise from mitochondria, that the latter first become reduced in size to a minuteness which renders them invisible, and that this is followed by a change in constitution and a gradual increase in size. Mitochondria are

sometimes minute to the limits of visibility and yet retain the characteristic staining reaction with janus black No. 2. The most minute degeneration granules, on the other hand, exhibit the same characteristic coloring with neutral red seen in the larger granules. It is perhaps important to note in this connection that those minute mitochondria are not always or usually found in fibroblasts that are just beginning to show the minute neutral red granules. It is only in the later stages of degeneration that the normal mitochondrial threads and rods tend to break up into granules.

THE RELATION OF GRANULE AND VACUOLE

It is not always possible to distinguish the granule from the small vacuole, as the granule may occupy practically all of the vacuole with only a thin rim of fluid. It may be that all the granules we are considering are included in vacuoles. The fact that granules are often irregular in outline would not nullify such a contention, since vacuoles themselves are sometimes irregular. It is conceivable that even the smallest granule may be surrounded by a rim of fluid too thin for detection. In our present state of knowledge concerning these bodies it is of no particular consequence whether all granules lie within vacuoles or all vacuoles contain granules. Practically all vacuoles do contain granules, one or several, and it is uncertain whether vacuoles exist that are entirely free from granules. We do not know why the vacuole should develop around the granule. It may be that minute vacuoles appear first and granules develop within them, or the granule may appear first and the vacuole develop about it. Since we are not certain of the exact relations when the granules have attained visible size, the ultramicroscopic condition must necessarily be still more uncertain. The impression one gets from the study of numerous specimens is that many of the granules in the healthy cell are free from vacuoles, and that the latter subsequently develop about them. The granules in the smaller vacuoles often appear to be larger than those in the large ones. The larger vacuoles, however, usually contain several granules, with perhaps an aggregate of material equal to the larger granules of the smaller vacuoles.

In vacuoles of the same diameter containing solitary granules, the latter often vary in size. The amount of fluid in the larger vacuoles is much greater in proportion to the size of the granules than that in the smaller vacuoles.

Multiple granules within vacuoles can be conceived of as arising in at least four ways: (1) By the coalescence of smaller vacuoles each with a single granule, the number of granules in the larger vacuole depending upon the number of smaller vacuoles which coalesce; (2) large granules may split up into small granules; (3) new granules may develop in vacuoles, by a process of crystallization, for example; (4) granules free in the cytoplasm might be taken into the vacuole as it enlarges.

THE POSITION OF ORIGIN OF THE GRANULES AND VACUOLES

We have not been able to determine the position of origin of the granules and vacuoles. In the early stages they are

scattered, but as they become more numerous, most of them are located in the immediate region of the centriole. Since they move about freely in the cytoplasm, either towards the centriole or away from it, one might conclude that they form in the more peripheral regions of the cytoplasm and are carried towards the centriole where they tend to accumulate, or that they arise near the centriole and are carried outwards into the more peripheral regions of the cytoplasm. The difficulties of the problem are increased by the fact that the smallest granules are on the boundary of visibility, and from that one must conclude that they begin their existence in the cells as dust-like granules invisible even with the highest powers. Such granules in cytoplasm would be unlikely to be found in their position of origin when they attain the size of visibility. The fact that they accumulate about the centriole may indicate only that they are carried there, as they form, by cytoplasmic currents, if such currents exist; and that these currents tend, during degeneration, to flow more towards the centriole than away from it. Such a view receives some support from the changes which occur about the centriole. We have noted elsewhere that the centrosome increases in size during degeneration, and that about it a centrosphere develops which gradually increases in size until it may become as large as the nucleus. The enlarging centrosphere is usually free or nearly free from granules and vacuoles, the latter surrounding it in a zone of varying thickness.

In cells with many vacuoles and a large centrosphere, the latter is sometimes filled with enormous numbers of the finest, dust-like granules which stain red with neutral red. What relation these bear to the granules under discussion is not known, but very likely they represent a similar degeneration product. We have seen that the ordinary degeneration granules begin to form before the centrosphere appears; thus they may arise independently of it.

THE MOVEMENTS OF THE GRANULES AND VACUOLES

The granules and vacuoles exhibit a considerable amount of movement, different from and more extended than the ordinary mitochondrial movements. It is irregular, sometimes rapid and jerky, sometimes slow and of varying speed. The distances traveled differ greatly; in general, the direction is from the region of the centriole or centrosphere to the periphery, or *vice versa*. The amount of activity varies in different cultures and in cells of the same culture, and is apparently easily affected by environmental factors. Under certain conditions no movements of the granules are to be seen. These movements are probably not dependent upon the activity of the granules themselves, but upon either cytoplasmic currents in which the passive granules are carried or metabolic changes. It has not been possible to see cytoplasmic currents.

As stated above, the movements of the granules are somewhat different in character from the mitochondrial movements; the amplitude is often greater and they are more lively. The movements are best followed in cells where the granules are stained red with neutral red and the mitochondria

blue with janus black No. 2. A red granule is sometimes seen passing along close to a blue-black mitochondrion, sometimes extending beyond the extremity of the mitochondrion. Again the granules may pass back and forth in paths that are some little distance from a mitochondrion, and may cross at varying angles above or below a mitochondrion. Sometimes granules are deflected by the mitochondria as the latter are bent, or appear to be bent, by the flowing granules. These appearances are such as to suggest that the granules are located in a more fluid, streaming part of the cytoplasm, while the mitochondria are in a less fluid part, the movements of which would be of a different character, thus giving to the mitochondrion and to the granule each its own peculiar type of motion. On the other hand, the different types of motion may be due entirely to the differences in composition of the mitochondria and of the granules, with a resulting difference in the interaction between them and the enclosing cytoplasm.

CHANGES IN THE FORM OF THE VACUOLES

The vacuoles vary not only in size and position, but also in shape. In some cells they are constantly altering their form such changes often occurring coincidentally with change of position. Frequently many or almost every cell in a culture will show vacuoles that are constantly changing both form and position. Again, very few if any of the cells will show such changes.

The variations in shape which the vacuoles may assume are quite remarkable. The usual form is spherical. This is the most stable condition and such vacuoles may remain unchanged for a long time. In contrast to this may be found a complicated, thread-like network of channels, very unstable and constantly changing. Between these two extremes a multiplicity of forms occur in different cells. The most common change is the sending outward from a vacuole of a long thread-like channel or process. This apparently contains fluid similar to that within the vacuole. These processes are likewise constantly changing their position and length. The entire vacuole may be converted into such a channel, which in rare instances may branch and anastomose with other similar channels to form a more or less complex network with granules scattered here and there within the channels. In such specimens the granules frequently are larger than the diameter of the channel and produce a distinct bulge in its wall. The granules are often observed to shift along the channel.

These vacuolar channels are very unstable and change much more rapidly than the mitochondria. Many of them are about the same size and shape as the mitochondria, and at first may prove to be somewhat confusing; but with the use of neutral red and other vital dyes (methylene blue and brilliant cresyl blue) they can be sharply and clearly separated from the mitochondria. Their behavior, too, is so different that one soon comes to recognize that they are entirely different. The vacuolar channels may change back into spherical or oval vacuoles.

I should suppose that these various changes in the form, and perhaps also in the position of the vacuoles, are dependent upon the metabolic activities, or upon the interchange of substances between the exterior and interior of the cell. The long processes and networks also suggest that there may be some relationship between vacuoles and the canalicular apparatus found in some other types of cells.

MITOCHONDRIA AND MITOCHONDRIAL VESICLES

In the vigorous, healthy fibroblast the mitochondria are usually scattered throughout the cell as long threads or rods, often branching or anastomosing and running in lines more or less parallel to the long axis of the cell; in others, radiating somewhat from the nucleus and centriole towards the periphery. As the granules and vacuoles increase in number the radial arrangement of the mitochondria about the centriole becomes more and more marked. In the earlier stages the mitochondria extend beyond the granular and vacuolar area into the clear cytoplasm. In some of the cultures the mitochondria come to lie in the cytoplasmic net between the vacuoles, and also partly in the clear peripheral regions at the ends of the cells. In such cells, even though the entire cytoplasm becomes packed with vacuoles and granules, the mitochondria may remain as short threads or rods until the cell is about to die.

Other cultures show fibroblasts in which the mitochondria undergo much more change. As the vacuoles and granules increase in number the mitochondria show more of a tendency to break up into short rods and granules, and these in turn may swell up into spherical bodies or vesicles of various sizes. The granules form very minute vesicles and the longer rods may form vesicles as large as the neutral red vacuoles.

These changes apparently begin first in the mitochondria lying immediately about the centrosphere and gradually extend toward the periphery. They are usually preceded by changes in the mitochondria which give them an irregular appearance, and the longer threads seem to be broken up into short rods. The irregularities of the mitochondria gradually become more marked and are chiefly characterized by differences in the diameters of the various threads and of the different parts of the same thread or rod. These changes are also accompanied by irregularities in the staining; that is, the mitochondria exhibit lighter and darker areas, especially with such stains as janus black No. 2. Under ordinary conditions of the culture, these changes in the mitochondria indicate degenerative changes in the cell. Similar changes can be brought about in a relatively short time in the long thread-like mitochondria of healthy fibroblasts by the use of potassium permanganate. With a 1-20,000, 1-40,000, or 1-80,000 solution there takes place with varying degrees of rapidity, depending upon the strength of the solution, changes in the mitochondria similar to those observed in the more slowly degenerating cells of the cultures.

During these changes both the thread and rod-like mitochondria and the mitochondrial vesicles stain bluish with janus black No. 2, and never at any time do they take up the

neutral red. In fact, there is always a sharp distinction between the staining of the mitochondria and the mitochondrial vesicles with janus black No. 2 and the staining of the degeneration vacuoles, the granules, and the processes of the vacuoles with neutral red. There are undoubtedly at times certain similarities between the two types of vacuoles when unstained, and in our earlier observations we were uncertain as to the relationship existing. For example, one often sees a small vacuole with a long mitochondrium-like process that is continually changing in shape, size and position. Now both the mitochondria and the neutral red vacuolar processes are subject to constant changes in form, size, and position. As mitochondria form vesicles the vesicular enlargement often takes place first at one end of the mitochondrium; the length of the unchanged narrow portion would vary, of course, with the length of the original mitochondrium and the size of the vesicle at the time of the observation. In unstained living cultures it might be impossible for the untrained eye to distinguish between such a changing mitochondrium and a neutral red vesicle with a mitochondrium-like process. With the application of a 1-10,000 solution of janus black No. 2 the mitochondria and the mitochondrial vesicles are stained bluish, whereas the neutral red vacuoles and granules remain unstained. If this stain is followed by a 1-25,000 solution of brilliant cresyl blue, it will be seen in a few minutes that the color in the mitochondria rapidly disappears, while the previously unstained vacuoles and granules take up the brilliant cresyl blue and appear bluish or violet in color. If, however, the janus black No. 2 is followed by neutral red (1-20,000 or 1-25,000), the blue color of the mitochondria and the mitochondrial vesicles is often increased in depth, while the previously unstained vacuoles and granules take up varying amounts of the neutral red dye. Then, too, the differences in the behavior of the two types of vacuoles when stained and followed with the application of potassium permanganate or chloroform indicate that we are dealing with two quite different things.

In some cells with almost complete vacuolization the mitochondria may show very little sign of degeneration or change, but appear as rods and short threads in the cytoplasmic network between the vacuoles. In some of the long spindle cells vacuolization may be complete at one end of the cell and the mitochondria be more or less broken up into rods and granules; while at the other end, the nucleus lying between the two parts, there may be almost complete absence of vacuoles and granules, and very little change in the long thread-like mitochondria. The degenerating end of such a cell seems to be always the end containing the centriole.

CHANGES IN THE REGION OF THE CENTRIOLE

As the cultures get older there is a gradual increase in the number and size of the granules and vacuoles. Parallel with this increase very important changes take place in the region of the centriole. As the granules increase in number, they tend to accumulate about the centriole, which is located near one side or one end of the nucleus. This gradual accumulation

of the granules, and later of the vacuoles, about the centriole gives a very characteristic picture, especially when the granules and vacuoles are stained with neutral red. One is often unable to recognize the centriole in the earlier stages in the living cell. In fixed material the centriole can usually be seen at the center of the mass of granules and vacuoles. Later, as these accumulate, the centriole becomes surrounded by a more or less clear area (the centrosphere) near the center of the mass of granules and vacuoles, and near one side or one end of the nucleus, with which it is more or less in contact. As the granules increase in number, the centrosphere increases in size, and at its center can usually be detected the double centriole. The centrosphere is usually entirely free from neutral red granules and vacuoles. It gradually increases and may eventually attain a diameter equal to, or even greater than, that of the nucleus. With its enlargement the granules and vacuoles appear to be pushed farther and farther away from the centriole. The centrosphere usually presents a clear medullary zone immediately about the centriole or centrioles, and a much wider cortical zone, which often shows radiations. Occasionally one or two small neutral red granules appear to lie within the centrosphere. In some cultures which have been stained with neutral red the centrosphere shows many very fine, red, dust-like granules. Since this seems to occur only in cells that show somewhat advanced vacuolar degeneration, it may be that it is indicative of the beginning degeneration of the centrosphere.

We have already considered the radial arrangement of the mitochondria about the centriole and centrosphere; the granules and vacuoles, lying between the mitochondria, also at times assume a more or less radial arrangement. We have considered also the movements of the granules and vacuoles which take place more or less in paths between the centriole or centrosphere and the periphery. The accumulation of granules, vacuoles, and mitochondria about the centriole, and the accumulation or building up of an increased amount of what seems to be a special type of cytoplasm about the centriole, would indicate that its activities are in some manner increased during the degeneration of the cells.

DISCUSSION

I venture to suggest that in due course of time it will be found that the living part of the cell cannot be stained by any of the so-called vital dyes, since the combination of the dye with the living protoplasm would so upset the delicate molecular constitution of the latter as to kill it; and because living protoplasm is so constituted that it cannot combine, either physically or chemically, with any other substances except such as are synthetically built up into itself. The corollary will be that the so-called vital dyes stain only the non-living cytoplasmic inclusions, such as granules, vacuoles, secretion granules, food-globules, mitochondria, etc.

One might well hesitate to class the mitochondria with non-living cytoplasmic inclusions, in view of the many claims that have been set forth as to the rôle of mitochondria in the transmission of hereditary qualities, and above all as to their part

in the formation of various cell structures during histogenesis. They are supposed to form the collagenic fibers (Meves), myofibrils (Benda, Meves, Duesberg, Hoven and others), epidermal fibers (Firket and Duesberg), neurofibrils (Hoven, Meves and G. Arnold), and secretion granules (Grynfeldt, Bobeau, Regaud and Marvis, Nicolas, Regaud and Favre, Hoven and others)—a formidable list of authors imbued with the idea that the mitochondria possess magic qualities. Cowdry, in his recent excellent contribution, "The Mitochondrial Constituents of Protoplasm," states that "the radical claims concerning their rôle in histogenesis have forced the reinvestigation of the entire field." He is inclined to believe that the mitochondria are concerned, either directly or indirectly, with metabolism or with protoplasmic respiration. The mitochondria may well play an important rôle in the general metabolism of the cell, more especially in that particular part of the metabolism which is common to all cells, such as respiration, perhaps, as has been suggested by several authors (Kingsbury, Mayer, Rathery and Schaeffer). The mitochondria might play such a rôle in the general metabolism of the cell and still not be considered as a part of the living cytoplasm, any more than are the stored-up yolk-granules found in many eggs.

Coghill suggests that during the process of digestion and assimilation of yolk in amphibian embryos certain end-products of the process segregate into what he calls *alpha bodies* and *beta bodies*, and that the former, probably undergoing some chemical change, become free as mitochondria in the process of assimilation into protoplasm. Whether this be true or not, more interesting still is the suggestion that the more toxic action of janus green (which stains the mitochondria), as compared with that of neutral red (which stains the beta bodies), is due to the fact that the processes leading up to the construction of protoplasm are obstructed by the reaction of this stain; whereas, only the residue, so to speak, of these processes is attacked by the neutral red. If the mitochondria are concerned in the respiration of the cell, the action of janus green on the mitochondria, for which it has a special affinity, might obstruct the respiration to such an extent as to kill the cell. Coghill's suggestion as to the less toxic action of neutral red would apply to our conception that neutral red stains only the non-living matter, such as accumulated waste products or stored-up food-stuffs, or some partially digested food-stuffs that are not immediately essential to the cell.

Granules with a special affinity for neutral red have been described in many different types of cell in many different species of animals, and it will be interesting in this connection to consider a few of the more striking cases. Fischel ('01) found in the living ectodermal cells of amphibian larvæ many such granules. He considered them as living elements, in conformity, perhaps, with the views of Altmann prevalent at that time. We know that the ectodermal cells of various vertebrates deposit within themselves substances which are usually considered as non-living elements, and which in many cases ultimately accumulate to such an extent as to finally transform the cell into a non-living scale. The fact that such

deposits may serve a useful purpose in the organism does not invalidate the view that they are non-living inclusions.

The Clarks have described in the lymphatic endothelial cells of the tadpole's tail numerous granules which take up the neutral red in the living. E. R. Clark has shown that the lymphatic endothelium is actively phagocytic, and since these cells possess the power of taking up particulate matter it may well be that they also take in ultra-microscopic particles and segregate them into granules that take up the neutral red. Whether these granules are of this nature, or whether they consist of waste products, is of course impossible to determine at present. Other phagocytic cells, such as the elasmatocytes and leucocytes, are especially rich in vacuoles and granules that have a great affinity for neutral red. The elasmatocytes are especially interesting in this connection, as they are abundant in most of our cultures. Certainly the vacuoles, and probably all the granules which stain so avidly with neutral red, are non-living inclusions, the granules for the most part being derived from cellular debris taken up by the cells.

It is well known that the partially digested dead contents of the food vacuoles of protozoa stain with neutral red (Plato, Stole) and that disintegrating bacteria and cell debris in leucocytes stain in a similar manner (Plato, Arnold). Many eggs contain numerous granules and globules, probably food-stuffs, and perhaps accumulated waste products also, that stain with neutral red. The eggs of *Cerebratulus*, of the sand-dollar, and of *Lophius piscatorius* (M. R. Lewis), as also the amphibian egg (Coghill), have recently been studied with the aid of neutral red, and all were found to contain numerous neutral red-staining granules probably of the nature of stored-up food-stuffs.

There are reasons for believing then that the granules and vacuoles considered here are non-living cytoplasmic inclusions. Since the granules and vacuoles accumulate without noticeable enlargement of the cells, they must be formed in greater part from the cytoplasm rather than by the diffusion into the cell of substances and fluid from the outside; moreover, they are formed from the cytoplasm, presumably as products of the metabolism of the living cell. These products of metabolism may be divided into two classes—food products and waste or secretion products. The former are found most abundantly in egg and embryonic cells, and we should scarcely expect to find cells cultivated in Locke's solution storing up food-stuffs. We are led, therefore, to accept the alternative theory, *i. e.*, that the granules and vacuoles are accumulated waste products and that they are formed in part, at least, by the breaking down of the cytoplasm. This process may be looked upon as a degeneration phenomenon, since it ultimately leads to the death of the cell.

The altered environment of the fibroblasts in the cultures probably sooner or later interferes in many ways with their normal metabolism, either from the absence of oxygen, salts, or food-stuffs, or through the accumulation in the culture medium of waste products in sufficient amount to prevent their normal elimination from the cells by osmosis. This altered environment with its lack of certain essential salts, food-stuffs, and

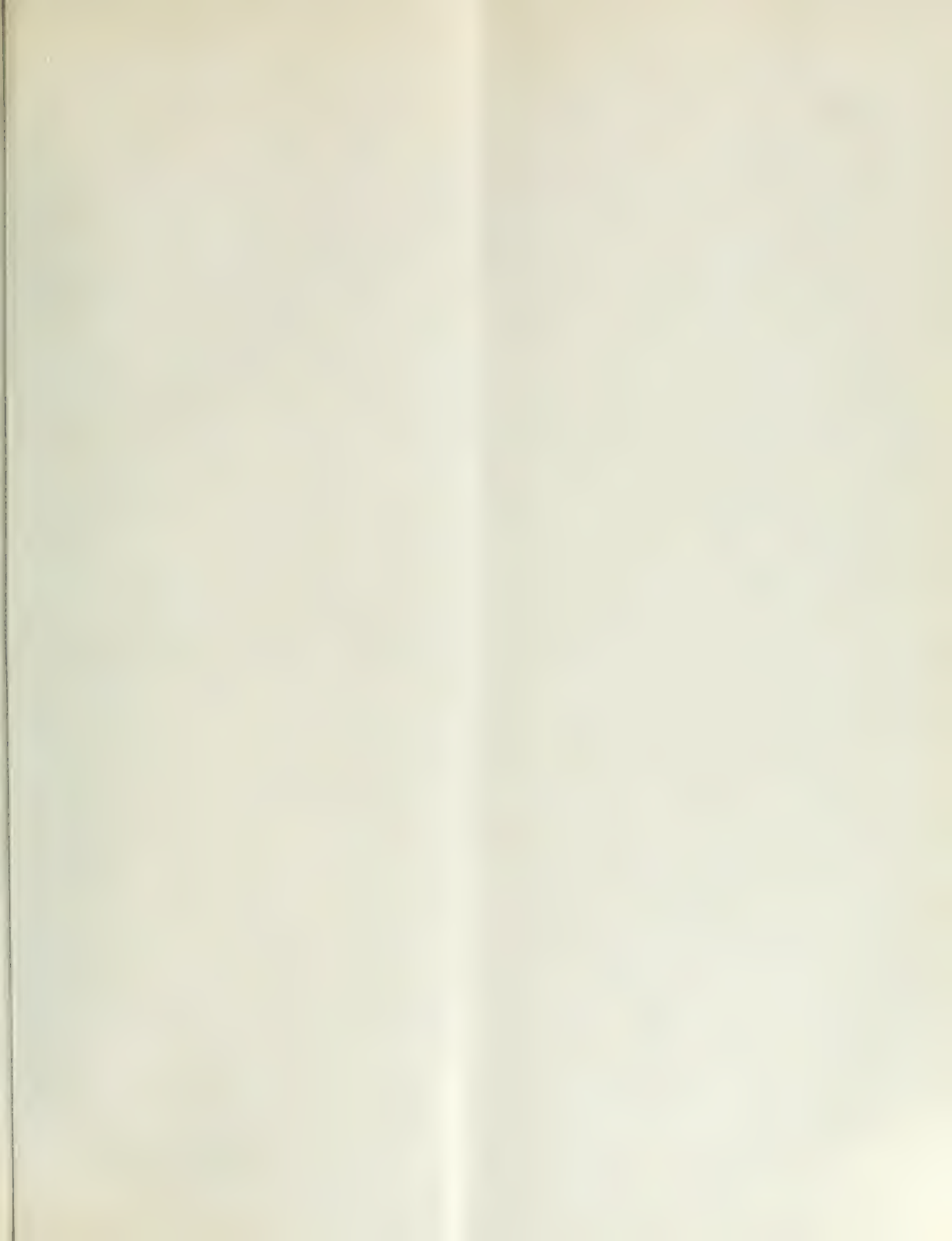
perhaps of oxygen, would favor the breaking down of the cell protoplasm through starvation, and the accumulation of waste products. We have no method of determining whether the contents of the vacuoles and granules are identical with the normal waste products excreted from the cell. An alteration in the composition of the waste products, however, might be expected to accompany the starvation of the cell.

Since the cells do not appear to increase in size as vacuolization spreads, we are more or less forced to conclude that part of the cytoplasm is broken down into granules and vacuoles. This process may use up most of the cytoplasm, leaving only a slender framework between the vacuoles. The enlarged centrosphere usually remains intact and does not become vacuolated. The cytoplasmic framework is continuous with the centrosphere, radiating out from it in all directions.

The relationship of the granules and vacuoles, and likewise of the mitochondria, to the centriole and to the gradually enlarging centrosphere is not at all clear, if we attempt to explain it in physiological terms. The anatomic picture is plain enough, but why the granules and vacuoles should surround the centriole and centrosphere is unknown.

The centriole and its centrosphere have long been considered by many authors as the dynamic center of the cell, the focal point of the more active archoplasm of Boveri, the kinoplasm of Strasburger, the spongioplasm of Leydig, etc. This peculiar cytoplasm, which accumulates about the centriole during degeneration and which I have also seen much augmented in amount in giant cells in certain cultures, seems to be different from the ordinary cytoplasm that occupies the bulk of the cell. Whether there is an actual increase in the amount of the stuff forming the centrosphere or merely a concentration of already existing material about the centriole, is difficult to determine. There appears, however, to be an actual increase.

Conklin speaks of the spongioplasm of the egg of *Crepidula* as "the interalveolar or continuous substance within which are found enchylemma, microsomes, mitochondria, as well as yolk, oil, and other inclusions." He finds that "large inclusions such as yolk spheres are forced out of regions where the spongioplasm concentrates." A somewhat similar phenomenon seems to take place about the enlarging centrosphere, where the vacuoles and granules are forced away by the concentration or increase in the archoplasm or spongioplasm about the centriole in the degenerating fibroblasts. The framework of cytoplasm, which extends from the centrosphere to the peripheral layer in these highly vacuolized fibroblasts, corresponds, perhaps, to the spongioplasmic framework in *Crepidula* that remains throughout the entire cell and connects the nucleus and centrosphere of the resting stages to the peripheral layer after the centrifugal force has displaced the more fluid part of the cytoplasm, the yolk, and the other cytoplasmic inclusions. It is the spongioplasm that seems to be the living part of the cytoplasm, the part which determines the polarity of the cell. In the normal fibroblast the cytoplasm, except for the mitochondria and a few granules, appears homogeneous. Does this apparent homogeneous cytoplasm consist of two parts,





a spongioplasmic framework and a more fluid enchyliema? Or is it all spongioplasmic material, except for the inclusions above noted?

The causes of, or factors concerned in, the gradual enlargement of the centrosphere are not known. It is well recognized that in many eggs where food accumulations are considerable the attraction sphere is large. It is also larger in cells that are about ready to divide than in the resting cell. There is undoubtedly a relationship between the accumulation of food-stuffs in the egg and the size of the attraction sphere; and again, between the growth in size of cells which are destined to divide and the increase in the size of the attraction sphere.

Is the accumulation of granules and vacuoles about the centriole the factor that causes the enlargement of the centrosphere? Such an accumulation of granules and vacuoles would naturally alter the usual relationship of the centriole to the periphery of the cell, upsetting the metabolic balance in such a manner as to cause, perhaps, the building up of the enlarged centrosphere, since the metabolic activities which are centered in the centriole probably depend upon a constant interchange of materials between the centriole and periphery. The accumulating waste products about the centriole in the form of granules and vacuoles would certainly tend to alter this.

BIBLIOGRAPHY

- Burrows, M. T., and C. A. Neymann: 1917. Studies on the metabolism of cells *in vitro*. Jour. Exp. Med., XXV.
- Clark, E. L., and E. R. Clark: 1919. On the reaction of certain cells in the tadpole's tail toward vital dyes. Anat. Rec., XV.
- Coghill, G. E.: 1915. Preliminary studies on the intercellular digestion and assimilation in amphibian embryos. Science, N. S., XLIII, 347.
- Conklin, E. G.: 1917. Effects of centrifugal force on the structure and development of the eggs of *Crepidula*. Jour. Exp. Zool., XXII.
- Cowdry, E. V.: 1918. The mitochondrial constituents of protoplasm. Contributions to Embryology, VIII, Carnegie Institution of Washington, Pub. No. 271.
- Fischel, A.: 1901. Untersuchungen über vitale Färbung. Anat. Hefte, Bd. XVI, 417.
- Lewis, M. R.: 1917. The effect of certain vital stains upon the development of the egg of *Cerebratulus lacteus*, *Echinorachnius parma*, and *Lophius piscatorius*. Anat. Rec., XIII.
- Lewis, M. R., and W. H. Lewis: 1915. Mitochondria and other cytoplasmic structures in tissue cultures. Am. Jour. Anat., XVII.
- Luna, E.: 1917. Note citologiche sull' epitello pigmentato della retina coltivato "in vitro." Arch. Ital. di Anat. e di Embr., XV.
- Maximow, Alexander: 1916. The cultivation of connective tissue of adult mammals *in vitro*. Russian Archiv of Anat., Hist. and Embryology, I.
- Plato, J.: 1900. Ueber die "vitale" Färbbarkeit der Phagocyten des Menschen und einigen Säugethiere mit Neutralroth. Arch. f. mikr. Anat., LVI, 868.
- Stolc, A.: 1902. Ueber das Verhalten des Neutralroths im lebendigen Protoplasma. Zeit. f. allg. Phys., I, 209.

EXPLANATION OF FIGURES

The figures are all drawn free hand from living cells stained with neutral red, and many of them with janus black No. 2 in

addition. The original drawings gave only vague outlines for the cells, as the author's attention was concentrated on the relations of granules, vacuoles, mitochondria, centriole, centrosphere, and nucleus. Since then the borders of similar cells, both in living and fixed material, have been examined, and appropriate outlines added to the original cell drawings. Thus the greater number of the figures are composites. The edges of most of the fibroblasts present a peculiar scalloped condition, with slender processes of varying lengths extending from the points, much longer, as a rule, than those shown in the figures.

Figs. 1, 2, 3, 4, and 5 are from 78-hour-old cultures; explants from the legs of 8-day chick embryos. Figs. 2 and 3 are from the same culture, the others are each from a different culture.

Fig. 1.—Healthy fibroblast with few granules. Figs. 2, 3, 4, and 5 show the gradual accumulation of granules about the centriole and the increasing radial arrangement of the mitochondria. In Fig. 5 are also seen many small vacuoles. Fig. 4 and 5 show small centrospheres.

Fig. 6.—A 74-hour-old culture; explant from leg of 9-day chick, showing increased number of vacuoles and granules about an enlarged centrosphere. Mitochondria broken up into short rods.

Figs. 7 and 8.—54-hour-old cultures; explants from leg of 8-day chick. In Fig. 7 the centrosphere is at the side of the nucleus and the granules, vacuoles and mitochondria are arranged more or less symmetrically and radially about it. In Fig. 8 the centrosphere is at one end of the nucleus. Very few granules or vacuoles are seen in the opposite end of the cell.

Figs. 9 and 10.—78-hour-old cultures; explants from leg of 8-day chick. The centrosphere either has not developed or is obscured by the crowded granules and vacuoles. The centriole was not seen, but its position in both cells is undoubtedly at the side of the nucleus.

Fig. 11.—A 78-hour-old culture; explant from leg of 8-day chick. Large centrosphere surrounded by granules, vacuoles, and mitochondria. Wide cortical zone of centrosphere shows radiations. The vacuoles in this cell were constantly sending out long processes.

Fig. 12.—A 48-hour-old culture; explant from the leg of a 7-day chick. Cell crowded full of large vacuoles, except at the thin edge. Mitochondria broken up into short rods which seem to lie in the cytoplasmic framework—centrosphere obscure.

Fig. 13.—A 48-hour-old culture; explant from leg of 7-day chick. Very large centrosphere surrounded by many large vacuoles. Radially arranged mitochondria, rather long rods and threads. No vacuoles or granules in the opposite end of the cell.

Fig. 14.—A 2-day-old culture; explant from leg of 7-day chick. Large centrosphere; entire cell crowded with large vacuoles; mitochondria in form of short rods.

Fig. 15.—A 3-day-old culture; explant from leg of 7-day chick. The vacuoles showed much motion and were constantly sending out long processes or changing into channels, which are seen to anastomose at one end of the cell.

Fig. 16.—A 24-hour-old culture from the leg of a 7-day chick. The vacuoles and granules showed considerable motion, and the vacuoles were constantly sending out processes and changing in form.

Fig. 17.—A 3-day-old culture from intestine of a 7-day chick. The mitochondria have all changed into vesicles. Degeneration has progressed to such an extent that the vacuoles have begun to disappear.

Figs. 18, 19, and 20.—2-day-old cultures; explants from the legs of 7- and 8-day chicks; showing variations in the vacuoles, centrosphere, etc. Centrosphere full of dust-like granules.

Fig. 21.—A 3-day-old culture; explant from leg of 9-day chick. Mitochondria are changing into vesicles.

SOME ASPECTS OF OVARIAN PREGNANCY. WITH REPORT OF A CASE

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Although the first case of ovarian pregnancy under that heading in the *Index Medicus* is that of Kouver ('97) (van Tussenbroek, '99), careful scrutiny of the titles listed for the last decade reveals the fact that 5 cases of ovarian pregnancy were reported in 1908, 4 each in 1909 and 1910, 7 in 1911, 13 in 1912, 9 in 1913, 7 in 1914, 3 in 1915, 1 in 1916, and 5 in 1917. This makes a total of 58 cases apparently reported within this decade. Since the reports on some of the cases were published in three different journals, these were, of course, counted merely as one, and although the authenticity of four of the cases must be questioned on the basis of the titles alone, the series, nevertheless, is a large one in spite of these facts and of a marked decline in the number reported during the war. Since Norris ('09) stated that only 19 certain cases, approximately only one-third as many as all cases listed in the last decade, were reported in the decade between 1899 and 1909, it would seem that ovarian pregnancy not only is receiving increasing attention, but that a change in attitude probably is in progress. This conclusion would seem to be justified even though a careful examination of the descriptions of the cases reported in the decade between 1908 and 1917 would reduce somewhat the number listed.

Lockyer ('17) accepted as authentic only 22 cases of those reported between 1910 and 1917, but his review is only a partial one. Even so, it shows that there is a decided increase in the number of cases which have been regarded as genuine from decade to decade. The marked increase in the number of genuine cases reported in recent decades becomes still more evident if one recalls that Williams ('10) found only 13 positive cases up to 1906, whereas Norris found 19 positive cases in the single decade between 1899 and 1909. That is, Norris found more positive cases reported in this decade than had been reported in all previous medical history up to 1906. This surely is a significant fact.

The opinion that many, even if not all, cases of so-called hematocele, hematoma, apoplexy, blood cysts, and rupture of the ovaries, probably are nothing but cases of ovarian pregnancy in disguise, has been held by various investigators for some time. Hence, if hematocele of the ovaries repeats the history of hematosalpinx, it is not unlikely that the near future will see a marked increase in the reported frequency of "a fact so curious and important in itself," as Granville aptly put it a century ago. This would seem to be true in spite of the fact reported by Norris and Mitchell ('08), that only a single case of ovarian pregnancy was found among 44 extra-uterine specimens and 58 hemorrhagic cysts contained in the collection of 1700 gynecological specimens at the hospital of the University of Pennsylvania. At any rate, a careful microscopic examination of all such cases would seem

to be indicated in the future in order to determine, if possible, which cases are, and which are not, conceptual in origin.

To-day it is no longer true, as stated by Freund and Thome ('06) and by Sencert and Arom as late as 1914, that authentic cases of ovarian pregnancy belong to the great rarities. Yet the fact that many of our states, as well as many large clinics, have not a single case on their records seems to suggest that the condition still is seldom recognized, a century after Granville observed his first case. Moreover, a number of continental gynecologists and obstetricians, for a quarter of a century, have regarded the occurrence of ovarian pregnancy as undoubted. Anderson ('17) stated that German writers began to report cases of ovarian pregnancy with some frequency after 1901, and Gilford ('01) also called attention to the fact that continental opinion long had accepted ovarian implantation not only as possible, but as proven. Gilford further referred to the often quoted opinion of Tait that ovarian pregnancy is as rare as "A blue lion or a swan with two necks," and in his article in 1899 also called attention to the opinion of Bland-Sutton, that ovarian pregnancy not only has no existence, but that it is impossible. These opinions are particularly interesting in view of the careful reports made by Granville (1820 and 1834), in connection with the two cases which he then and which others since have regarded as cases of undoubted ovarian pregnancy, in spite of the absence of microscopic examination. In view of this lack it is particularly fortunate that both of these reports of Granville are accompanied by splendid illustrations by Bauer, which also won his praise and admiration and which greatly strengthened his cases. It may be recalled in this connection that Werth ('01) accepted Granville's case recorded in 1820, but said nothing about his second more convincing instance reported in 1834.

Although there is as yet no agreement as to what constitutes an authentic case, a review of the literature justifies the growing and apparently well-founded belief that in the past too much emphasis has been laid on certain criteria which later experience has shown to be partly inapplicable. It is becoming clear that some cases, formerly excluded for reasons regarded as sufficient, with our present knowledge could no longer be rejected. Moreover, it does not seem at all improbable that some cases listed as *tubal* really were *ovarian* in origin. Nor must it be forgotten that not even the entire absence of remnants of the conceptus can positively exclude a case from the category of true ovarian pregnancy. In a number of cases in the literature, and also in the present case, the clinical history and gross anatomic findings suggest the conclusion drawn by Scott ('01) on *a priori* grounds alone, that the conceptus may be completely resorbed. It may, of course, also be aborted and disintegrate completely. That such an

assumption is justified is indicated by the lysis of the embryo or fetus in a large number of cases of ovarian pregnancy, and also by the very degenerated condition of some of the vesicles and of the surrounding ovarian stroma. The possibility of such an occurrence is established also by similar events in the uterine and tubal pregnancies discussed elsewhere (Meyer, '19), and probably is illustrated by such cases as those of Auning and Littlewood ('01), in which no mention is made of an embryonic disc in a translucent conceptus the size of a "pea." Then, to be sure, there are the cases of unruptured ovarian pregnancies containing villi only, as well as the rare case, probably of double ovarian pregnancy, of Holland ('11). Although one cannot be certain that embryonic tissue was removed from the left ovary with the blood-clot which was forcibly expelled at the time of operation, it is not at all improbable that the small plasmodial masses found in the left ovary were the only remnants of the conceptus. I realize fully that the conclusion that young conceptuses may be wholly dissolved is fraught with great uncertainty, but I am quite sure that it is justified by the facts, and that it therefore is in the direction of truth. It could only fail to be so if every ovum that becomes implanted within the ovaries were aborted or were removed by operation before lysis was possible.

One cannot rightly refuse to recognize the possibility of the spontaneous disappearance of an ovarian pregnancy. Since implantation in the ovary occurs under such abnormal conditions, it would seem that for this reason alone the great majority of such implantations inevitably must succumb. This would seem probable wholly aside from considerations regarding the development of the corpus luteum, although lack of, or interference with, the development of the latter also would seem to condition early death of the conceptus if the results of the long series of experiments on rabbits by Frankel ('03-'10) are indicative of the rôle played by the corpus luteum in early implantations in man also. It surely is difficult, if not impossible, to see how implantation within the Graafian follicle, and especially the later development of the conceptus, can fail to interfere with the development of a normal corpus luteum. Cases in the literature, and also in the present case, did not reveal the presence of any well-preserved or even true luteal cells at the time the pregnancy was terminated. Although this fact does not presuppose an entire lack of development of these cells in the earliest stages of the implantations, it undoubtedly does imply a defective development, which in itself may have become responsible for the death of the conceptus. Nor should the possible toxic effect upon the conceptus of luteal cells be forgotten in this connection.

I do not assume, to be sure, that the clinical symptoms and signs alone should suffice finally to group a specimen as truly ovarian, but when these are indicative of the presence of an ectopic gestation, and when undoubted intra-uterine decidual changes are present, in the absence of abdominal pregnancy or tubal involvement and a normal corpus luteum, and the presence of a blood-clot within the ovary, there would seem to be little reason for doubting the authenticity of the ovarian implantation even in the absence of embryonic remnants.

Since changes suggesting decidual reaction in the ovary have been reported so seldom it is doubtful whether much emphasis can be laid on them. One seems justified in saying this in spite of the fact that the presence of decidua in the ovary formed the only anatomic evidence upon which Kantorowicz ('04) confidently classed his two rather advanced cases of ectopic pregnancy among the authentic. Moreover, if it be true, as stated by Webster ('04) that changes which cannot be distinguished from true decidual changes not infrequently occur in the ovary in connection with normal uterine pregnancies, then the presence of islands of decidual cells in an ovary surely cannot be regarded as indicative of ovarian pregnancy. I wonder, however, whether it would not be possible to distinguish genuine decidual cells by modern histochemical methods. In making this observation, I am fully aware that various criteria have been advanced from time to time by means of which to judge ovarian pregnancies, and that many of these have met with objection and have hence been modified. Such modifications would seem to be inevitable as long as there is progress in the solution of an unsettled question.

The absence of the fetus in many of the recorded cases in itself demonstrates the entire inapplicability of the criterion added by Jacobson ('08). Moreover, the histologic appearance of the ovarian tissue around certain portions of the blood-clot in the present, and also in some of the cases in the literature, would seem to suggest that it may be very difficult to find remnants of ovarian tissue at several points in a case of pregnancy which has advanced far. Hence, this criterion of Spiegelberg ('78) cannot be regarded as necessarily crucial. Whenever the implantation is developed at the outer instead of at the inner margin of a follicle, as in the case of Banks ('12), early destruction, even if not early rupture, of the overlying ovarian stroma and capsule would seem to be inevitable. Indeed, whenever the layer of ovarian stroma overlying the placenta is thin, very early death of the fetus would seem to be inevitable from defective nutrition alone. On the other hand, when placental development occurs in the region of the follicle directed toward the body of the ovary, great destruction of the ovarian stroma would seem to be unavoidable, even if something akin to normal decidual formation actually took place. In the case of Engelking ('13), for example, not a trace of an ovary was found in an ovarian pregnancy which had become interstitial. Even without assuming the complete authenticity of this rather equivocal case, it would seem highly probable that the presence of ovarian tissue later in the pregnancy probably is determined very largely by the location of the fertilized follicle within, or by the exact location of the implantation upon the ovary.

Werth ('87) is said to have collected 12 cases, among which he regarded only that of Leopold ('82) as authentic. Leopold ('99) reported 14. Gilford ('01), in a splendid succinct review of the literature, gave 28 cases, 16 of which he regarded as undoubted and 12 as probable. Roche ('02) accepted only 12 cases. Füh ('02) accepted 21. Kantorowicz ('04), using the criteria of Leopold ('99), together with a microscopic examination as a basis, grouped the cases in the literature as

certain, probable, and uncertain. He considered 17 as certain, 10 as probable, and 13 as uncertain. And to the 17 cases regarded as certain by him, Kantorowicz then added two of his own, basing his decision, however, mainly upon the presence of decidua in the ovaries, thus making 19 cases regarded as authentic by him. Freund and Thome ('06) regarded 23 of all the cases reported up to that time as certain. Norris and Mitchell ('08) considered 16 as positive, 15 as probable and 9 as fairly probable. Warbanoff ('09) collected 34 cases and Norris ('09) regarded 19 of those contained in the literature of the previous decade as positive; but Williams ('10), from a critical review of the literature up to 1906, and upon the basis of the criteria of Spiegelberg, regarded only 13 as positive, 17 as highly probable, and 5 as probable. Mapes ('14) collected 30 cases, but wholly from secondary sources, and Lockyer ('17) 42, from the years 1910 to 1917. Of these cases Lockyer accepted 22 as authentic and 20 as questionable and undecided from the evidence available to him.

This short summary suffices to show that there is as yet no consensus of opinion as to what constitutes an ovarian pregnancy. Although this fact finds its explanation partly in our lack of sufficient knowledge, it is due also to the meagerness of some of the reports. Besides, if complete disintegration and lysis of intraovarian conceptuses can occur, then it must always remain a question of opinion in the future whether some of the cases so reported really were or were not true ovarian pregnancies. This must remain true no matter how thorough the microscopic examination, unless the clinical history or changes in the maternal organism can afford us crucial tests in such cases.

Anyone who reads far into the literature of ovarian pregnancy also must become aware of the fact that even very recently skepticism has been carried too far. Jacobson ('08), for example, placed the case of Kouwer-van Tussenbroek (a case which finally convinced Bland-Sutton) and that of Webster ('04) in the doubtful class! Furthermore, Jacobson also insisted upon the presence of an embryo or fetus as absolutely essential.

It must be emphasized, however, that even a liberal attitude on the part of a reviewer would not justify him in accepting all cases reported as genuine upon the basis of the reports themselves, for they—especially the older ones—often are too meager to enable one to form a reliable opinion. This is illustrated also by such recent reports as those of Garrard ('16), Martin ('17), Sweeney ('17), and of Mills ('17). Although it must be remembered that from the very nature of things it sometimes is impossible to make a report which in itself carries conviction, it is regrettable that in a number of relatively recent cases in which such a report apparently could have been made, this was not done. Mills' case seems to have been an instance of ovarian implantation in a region other than the Graafian follicle, and hence recalls the first case of Granville and the cases of Franz ('02), Norris ('09), Paucot et Debeyre ('13)?, and perhaps also that of Kouwer ('97) (van Tussenbroek, '99).

From evidence contained in the literature, it is clear that further reports of single cases are not needed for the purpose

of emphasizing the occurrence of ovarian pregnancy, yet such reports nevertheless may help in the determination of the relative frequency of this novel and sinister condition, and also throw further light upon its genesis and the finer relations of the implantations, as well as upon other matters. Moreover, since the cases which are accompanied by a careful histologic examination and which for this reason alone are wholly unequivocal from an anatomic standpoint still are relatively few, the report of an additional case would seem to be justified. The present specimen (Carnegie Collection, No. 1522) was donated by Wynne to the Department of Embryology of the Carnegie Institution of Washington, and the following clinical report furnished by him:

CLINICAL HISTORY

GYN. No. 22303.—The patient, an Italian woman of 37 years, was admitted to the Gynecological Service of The Johns Hopkins Hospital July 12, 1916, complaining of pain in the lower abdomen, nausea and vomiting.

Family History.—Negative.

Past History.—General health good. She has never had any serious illness. For the past five years following a labor she has had recurring mild attacks of pain in the abdomen without nausea or vomiting.

Menstrual History.—Always regular every month except when pregnant or lactating. Duration four to five days; painless, moderate flow. Last period June 25, 1916. Last preceding period March 16, 1916. No intermenstrual bleeding before present illness.

Marital.—Married 18 years; seven children, oldest 16, youngest born 1½ years ago (died, 1915). Has had three miscarriages. History of labors and puerperia vague.

Present Illness.—Began five days ago (July 7, 1916) with sudden pain in lower abdomen, nausea and vomiting. She has had marked dysuria and painful defecation. For 12 hours after onset there was rather profuse bleeding from the vagina and there has been a bloody vaginal discharge since.

(The patient does not understand English and her husband acted as interpreter.)

Physical Examination.—T. 101.6° F. P. 96. R. 20. W. B. C. 8400. Hbg. 46 per cent.

The patient lies in bed grunting with pain. The skin is pale. The lips and mucous membranes are quite pale. There is a systolic blow heard at the apex and increasing toward the base, being loudest over the pulmonic area.

A drop of clear fluid was expressed from the right breast.

The abdominal respiratory movements are limited, although she does not complain of pain on deep inspiration. The flanks bulge somewhat. There is no demonstrable movable dullness. There is tenderness all over the abdomen, most marked over the lower left quadrant. There is increased resistance over the lower abdomen, but no muscle spasm. No masses can be made out.

There is a profuse bloody vaginal discharge. The cervix is pushed up behind the symphysis by a soft, exquisitely tender mass, filling the cul-de-sac. No crepitus is made out. Rectal examination confirms the vaginal. The fundus of the uterus is not felt.

July 13, 1916.—Ether examination.

There is a dark, bloody discharge from the vagina. There is no vaginal cyanosis. The cervix is lacerated, firm, and normal in size. The fundus of the uterus is about normal in size and is in anteversion. A boggy mass fills the cul-de-sac and to the right of the uterus a fairly firm mass, the size of a small orange, which is somewhat movable, can be felt. Definite blood-clot crepitus can be felt on rectal examination.

Pre-Operative Diagnosis.—Extra-uterine pregnancy, ruptured.

Operation (Dr. W. R. Holmes, Resident Gynecologist).—A free midline incision was made below the umbilicus. The peritoneum

was blood-stained. The abdomen contained 200 to 300 c. c. of dark fluid blood and clots, and a large clot filled the cul-de-sac. Active bleeding had ceased. The left tube and ovary were normal and free of adhesions. The right tube, which was quite normal in appearance, lay over a mass which had replaced the right ovary. This mass was roughly spherical, 5 to 6 cm. in diameter and semi-solid in consistency. Over the surface there were six or eight nodular projections, about 1 cm. in diameter. At the top of one of these projections there was a very small opening, from which bloody fluid could be squeezed. The surface of this mass was white with spots of bluish-black discoloration.

The appendix was normal except at the tip, where it was adherent to a blood-clot.

The tumor was removed by clamping, tying, and cutting into the right infundibulo-pelvic ligament and the right utero-ovarian ligament. The right tube was not removed. The appendix was also removed and all blood and clots were cleaned out of the abdomen. The incision was closed without drainage. At the close of the operation, the uterus was curetted. The uterine cavity measured 7.5 cm. in length.

A subcutaneous salt solution infusion was started on the table and continued on the ward until 2000 c. c. had been absorbed.

The patient was in good condition at the end of the operation and made an uneventful recovery.

The urine on admission contained red blood cells, white blood cells, no casts, acetone, a trace of albumin and no sugar. Several days after the operation it was negative, except for a faint trace of albumin.

August 2, 1916.—Discharged in good condition.

Gyn. Path., No. 22346.—Normal endometrium from curettage.

A letter from the patient dated February 12, 1918, said that she had remained in good health since the operation and had given birth to a full-term child January 29, 1918.

Several features in this clinical history deserve comment. First among these is the menstrual age as compared with the size of the chorionic vesicle. Since the cross-sections of the latter measure 15 x 18 mm. and since it and the amnion are degenerated and devoid of an embryo, it is evident that the latter must have died a good while before the time of operation. Hence, the menstrual period reported for June 25, 1916, very evidently was not the last period before pregnancy supervened, but the first period which recurred after the death of the conceptus. Consequently, this pregnancy undoubtedly dates from near April 13, the time of the first omitted period. Moreover, the conceptus must have died long enough before June 25 to have made inhibition of the succeeding period impossible. It should be noted, however, that the original menstrual cycle apparently was broken, for with the customary inter-menstrual period of 28 days, menstruation normally would have fallen due on June 7 instead of June 25. Hence, the maintenance of the original cycle would have brought rupture of this ovarian pregnancy, as indicated by the symptoms, on July 7, in direct relation with the onset of menstruation. Nor does it seem unlikely that the hyperemia accompanying the return of menstruation on June 25, if such it really was, may have been partly responsible for the onset of a sufficiently large and persistent hemorrhage to cause the slight rupture indicated by the symptoms on July 7. It must also be remembered in this connection that cases of ovarian pregnancy have been reported in which menstruation was uninterrupted. But in the case of Chiene ('13), for example, the death of the conceptus may have occurred so early that the

succeeding period was not inhibited, and the same thing may be true of the case of Lea ('10).

Since the material from the curettage, done at the time of operation, showed the presence of a normal endometrium, the uterine decidua associated with this pregnancy must have been shed some time previously. Such a conclusion also would seem justified by the condition of the conceptus, which apparently was unable to prevent a return to the normal. The absence of decidua at the time of operation also suggests that what was reported as a return of normal menstruation on June 25 may have been hemorrhage accompanying the expulsion of the decidua.

Since, in the present case, the chorionic vesicle was so degenerated and so completely isolated in a large clot, and especially since no well-implanted villi were found in the sections and gross portions examined, it is not at all probable that the hemorrhage that caused the rupture was due to a contemporaneous invasion of the vessels by the fetal trophoblast, such as occurs in uterine and tubal implantations, and as has been actually described also in ovarian implantations by Franz ('02) and by others. In the present, and in similar cases in the literature, it would seem that hemorrhage was made possible also by degenerative changes in the highly vascular stroma of the ovary which had been greatly compressed and stretched by the proportionately large blood-clot, the organization of which would seem to have been precluded by its size alone.

The fact that relatively few unruptured ovarian pregnancies are recorded suggests that the old tenet that rupture is less likely the more advanced the pregnancy becomes, probably is open to serious doubt, as suggested by Banks ('12), who believed that the tubes can accommodate themselves more readily than the ovary. Banks stated that in the majority of cases of ovarian pregnancy rupture occurred in the first two or three weeks, and Caturani ('14) also expressed doubts regarding the dictum that rupture of the ovary is less likely the more advanced the pregnancy. No one will deny, I presume, that the symptoms of rupture may have been totally absent, as reported in the cases of Norris ('09) and Grimsdale ('13), but this does not imply that the ovarian stroma or the germinal epithelium still surrounded the full-term conceptus. Such an occurrence would be possible only if the ovarian stroma and the overlying germinal epithelium underwent an astonishing hyperplasia. Although such a thing is conceivable it is decidedly significant that no one has reported any such finding or observed the presence of mitotic figures.

Instead of undergoing hyperplasia the ovarian stroma in this case is found invaded, stretched, compressed, and degenerate, and the germinal epithelium is entirely absent. The fact that several observers have seen what they took for the fibrin layer of Nitabuch also shows that degenerative changes in the ovarian implantations may be extensive. Hence, it would seem to follow that the absence of symptoms of rupture merely may mean that the ovarian stroma and epithelium which happened to overlie the fetal membranes gradually have died and degenerated before being forced apart by the expanding conceptus or the increasing hemorrhage. That such

a sequence of events is possible would seem to be undoubted, and merely distension of the ovarian stroma until it completely surrounded a full-term pregnancy is hardly conceivable; whereas, the absence of pain upon the yielding of an exceedingly thin degenerate layer of ovarian stroma is quite conceivable.

That rupture may occur very early is exemplified also by the cases of Chiene ('13), Seedorff ('15), and especially by that of Anning and Littlewood ('01) and of Holland ('11). In such curious instances as that of Grimsdale ('13) one can hardly assume that the ovarian tissue was preserved about the entire conceptus, and it is not at all unlikely that full-term ovarian pregnancies, which, according to Warbanoff, supplied a surprisingly large percentage of all cases collected by him, will form a far smaller percentage in the statistics of the near future. Indeed, they already form a far smaller percentage of those reported up to the present, and the advances in diagnosis alone make it very unlikely that in the future many cases of ovarian pregnancy will advance far before being detected.

The present specimen, which had been hardened and cut before it came to my attention, is a firm, nodular, dark-colored mass, $26 \times 16 \times 11$ cm., shown in Fig. 1. In the gross, it especially recalls the specimens of Freund and Thome, Giles ('14-'15), Jäschke ('15), and Lockyer's ('17) second case. The exterior is smooth though bosselated and formed by a rather injected layer which is extremely thin, showing the blood-clot beneath, around the greater extent of the specimen. The surface layer is eroded over several small elevated areas in which the blood-clot underneath is exposed. Hence, the capsule may have been ruptured in several or only in one of the areas as noted at the time of the operation. Near the region of amputation through the mesovarium shown to the right in the figure and marked by the corrugations of the hemostat, the tissue overlying the clot becomes more opaque, thicker, and also more yellowish. Here it is studded with small cysts, the character of which in itself suggests ovarian tissue. The color of the area to the right also is suggestive, and the cysts later were found to contain a clear viscid fluid, so characteristic of cysts of the ovary. The location of the main portion of the ovarian stroma shows that implantation occurred near the mid-point of the free convex or posterior border of the ovary, and that the stroma forming the sides gradually was forced apart, not by the growing conceptus, except perhaps at the beginning, but mainly by the hemorrhage itself.

The major portion of the surface of the divided specimen shown in Fig. 2 is composed of blood-clot, the presence of which confirms the "blood-clot crepus" spoken of in the history. This clot contains an empty vesicle, the wall of which is formed for the greater part of its extent by a thin fibrous layer, except near the proximal or lower portion in the figure, where a thicker portion of ovarian tissue hoods the clot. Approximately only about one-third of the ovarian stroma seems to be preserved.

Near the exterior of the thicker portions of the latter, a small cyst with clear content is found directly beneath the

surface, as indicated in Fig. 4. The distal or upper portion in the figure shows the clot to contain an empty, smooth-walled, degenerate chorionic vesicle, such as is frequently seen in tubal clots.

Examination of the cut surface with the binocular microscope shows the presence of only a few isolated, degenerated, and some hydropic villi scattered through the clot. Examination of the chorionic vesicle shows the presence of only a few attached villi and that the amnion is fused to the chorion. Since the entire specimen obtained at operation is still covered by a layer of ovarian tissue which is unbroken save in a few very small areas, it is evident that we are dealing with a very good example of an undoubted ovarian pregnancy in spite of the absence of an embryo. The latter undoubtedly did not escape through the small rupture in the capsule, for the chorionic vesicle seems entirely intact. Although the absence of a corpus luteum in the opposite or left ovary was not especially mentioned, lack of comment would seem to suggest that none was present, for the ovary very evidently was examined. Hence, this implantation probably took place within the Graafian follicle itself, and not in some other area of the ovary.

Celloidin sections of the excised portion show that the blood-clot contains no fibrin and that it is composed of relatively fresh and fairly well-preserved blood in the region near the main body of the ovarian stroma. The latter is quite normal although decidedly vascular, and contains ova. The layer of the ovarian stroma which surrounds the clot becomes thinner and thinner the nearer the free border is approached. It also becomes more trabeculated, hemorrhagic and degenerate. No overlying layer of smooth muscle, as mentioned by Young and Rhea ('11) and also by Kantorowicz, was seen. Some infiltration with polymorphonuclear leucocytes is noticeable. Degenerate villi are scattered about in the blood and a few others are apparently still attached to the equally degenerate ovarian stroma. Trophoblast is absent on these, although some of the villi that lie isolated in the clot possess a very evident epithelium and also are associated with a few small masses of very degenerate syncytium. Only a few degenerate nonvascular villi are still seen on the chorion. Very little evidence of epithelial proliferation is present on these, despite the fact that the blood in which the vesicle is embedded is not very degenerate. This seems to suggest that the hemorrhage which caused the rupture of the ovary was comparatively recent, although the conceptus had been dead for some time. Some of the villi scattered about in the blood-clot are outlined by degenerate syncytium only, and nothing but small degenerate masses of the latter are seen on the chorionic membrane or lying about isolated in the degenerate blood found in other places. Nevertheless, the epithelium of the chorionic vesicle is thickened at several points. The amnion is fused with the chorion and both membranes are very degenerate and destroyed almost completely in several places. The surrounding ovarian tissue, which is markedly vascular and degenerate, shows infiltration in places, especially where it is stretched over the large clot. No fibrous layer bounds the implantation cavity, as in the case reported by Seedorff. The ovarian stroma merely

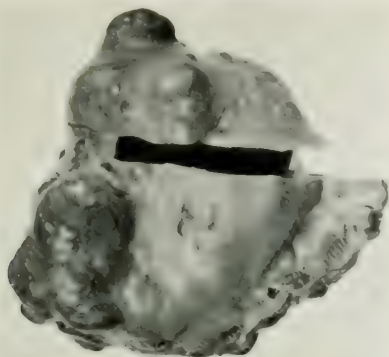


FIG. 1.—External appearance of the reconstituted gross specimen (Carnegie Collection, No. 1522). Natural size.

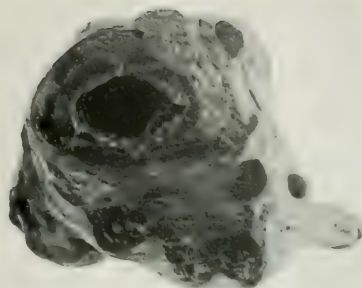


FIG. 2.—Appearance of cross-section of specimen shown in Fig. 1. $\times 1$.

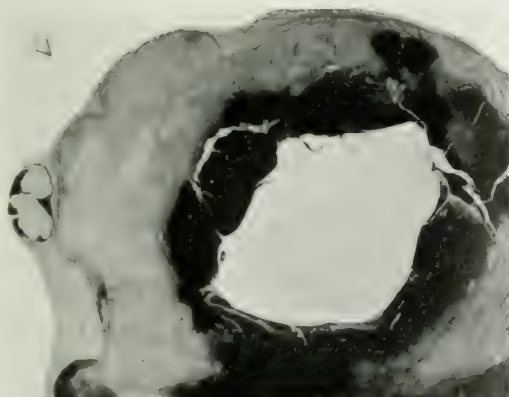


FIG. 3.—Photograph of a section from a part of the specimen showing the clot largely surrounded by ovarian stroma and containing the empty vesicle. The arrow points to the portion near which degenerate masses of what may have been lutein cells are found. $\times 2$.

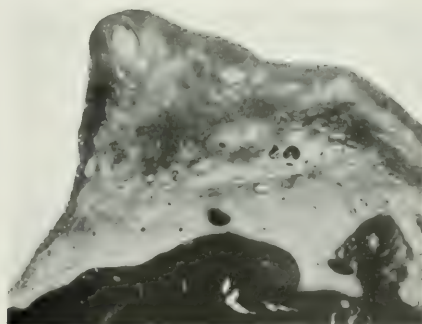


FIG. 4.—Photograph of a section taken from the thick portion of the ovarian stroma near the mesovarium, showing a well-developed Graafian follicle. $\times 3$.



slightly condensed here and there, and in places contains areas of hyaline degeneration, the exact origin of which could not be definitely determined. A few of these are found near the thin bounding layer of the ovarian stroma, but no lutein layer or even luteal cells could be recognized. The only objects seen which might be regarded as possibly luteal in origin are two microscopic rhomboidal areas which lie near a small depression upon the surface, indicated in Fig. 3. These areas, which were covered by a very thin layer of ovarian stroma only, were made up of parallel, degenerate, slightly separated cords consisting of a syncytium containing numerous rather pyknotic unequal-sized nuclei. No pigment was seen in these areas, and were it not for the arrangement of the syncytial cords, one would not be reminded even remotely of a possible luteal origin. Although the germinal epithelium was wholly absent in the areas examined, these questionable areas nevertheless may have had such an origin. In the absence of lutein cells the present case corresponds to that of Freund and Thome and others, and stands in marked contrast to the case of van Tussembroek, Franz, Anning and Littlewood ('01) and Thompson ('02). As in the case of Sedorff, no decidua was present and nothing suggestive of an attempt at decidual formation, as reported by Franz, Webster ('04 and '07), and Caturani and Kaetorowicz, was seen in the portions examined.

In describing his case, Sedorff declared that in some places of contact between the fetal and maternal tissues he could not discriminate between trophoblast and connective-tissue cells which looked like decidual cells and lutein cells. It is interesting that Sedorff also spoke of villi which were almost filled with Langhans' cells, an observation which naturally makes one wonder whether by any possibility these could not have been Hofbauer's cells.

The preserved ovarian tissue which was found near the amputation stump contained hemorrhagic follicles, as observed also by Mall and Cullen ('13). A Graafian follicle 3 mm. in section, shown in Fig. 4, protruded above the rest of the stroma and was quite mature. The presence of this follicle might be taken as an evidence of the occurrence of ovulation during pregnancy, were it not for the fact that the presence of so degenerate a conceptus shows that as far as any effect upon the maternal organism was concerned, the pregnancy virtually had been terminated long before. That both ovulation and menstruation can and do return after the death of an ovarian conceptus, but before its removal from the ovary, is illustrated also by cases in the literature, especially by that of Norris ('09). One must assume, however, that few, if any, surviving fetal elements can be present under these circumstances. This conclusion also would seem to be confirmed by the remarkable case of Sencert and Aron ('14). These authors reported a case of ovarian pregnancy in which nothing but a portion of an umbilical cord 5 mm. long containing Wharton's jelly, two arteries and a vein, and what was regarded as a placenta, remained. The latter was said to be composed of a narrow layer of plasmodium and a much thicker layer of trabeculated syncytial trophoblast containing blood between the trabeculae.

Because of the singular structure of this placenta and also because of the failure to find villi or any remnant of the membranes, the authors concluded that the chorionic vesicle therefore could not have reached the villous stage. How such a supposition can be reconciled with the survival of a portion of an umbilical cord entirely normal in structure, it is difficult to see. The ovary concerned was brown, of the size of a "large fresh walnut," and contained a tumor, apparently the so-called placenta, which was 2 cm. in diameter. Although these fetal remnants had brought about not only almost complete amenorrhea for two years and also atrophy of the ovary and uterus, ablation of the affected ovary was followed not only by a return of the menses, but by a normal pregnancy within seven months.

A second instance of ovarian pregnancy of special interest was that of Giles. No fetus was found, although the pregnancy was unruptured, and Giles estimated that the conceptus had died in the third or fourth week. The operation was not done until five months after the onset of the pregnancy. What is particularly interesting in this case is that Giles speaks of the mucoid degeneration of the connective tissue of the villi. The latter were found to be large, much branched, and had ramified in the clot. Since Giles also spoke of one of the illustrations as showing a vascular state of some of the villi, it seems possible that this was a case of hydatiform degeneration, even though there were no signs of activity of the syncytium. Since the fetal membranes were isolated in a blood-clot very much degenerated and the villi without a Langhans' layer, one scarcely could expect to find much evidence of epithelial proliferation so common (but not essential) in hydatiform degeneration. Giles estimated that four months had elapsed since death of the conceptus, and if this specimen really was a hydatiform degeneration, it is the first one observed in ovarian pregnancy and hence of particular interest for this reason alone.

REFERENCES

- Anderson, S.: 1917. Primary ovarian gestation. *Intern. Clin.*, XXVII, ser. 2.
- Anning, G. P., and Harry Littlewood: 1901. Primary ovarian pregnancy with rupture 14 days after last menstruation. *Trans. Lond. Obst. Soc.*, XLIII; and *Lancet*, 1901, 1.
- Banks, A. G.: 1912. A case of ovarian pregnancy. *Jour. Obst. and Gyn. Brit. Emp.*, XXI.
- Caturani, M.: 1914. Ovarian pregnancy with report of a case. *Am. Jour. Obst.*, XLIX.
- Chiene, G.: 1913. A case of ruptured very early primary ovarian pregnancy. *Edin. Med. Jour.*, N. S., X.
- Engelking, Ernst: 1913. Intraligamentar entwickelte Eierstockschwangerschaft. Ein Beitrag zur anatomischen Diagnostik vorgeschrittener Fälle. *Monatschr. f. Geb. u. Gyn.*, XXXVII.
- Franz, K.: 1902. Ueber Einbettung und Wachstum des Eies im Eierstock. *Beitr. z. Geb. u. Gyn.*, VI.
- Fraenkel, L.: 1903. Die Function des Corpus luteum. *Arch. f. Gyn.*, LXVIII.
- Idem: 1910. Neue experimente zur Function des Corpus luteum. *Arch. f. Gyn.*, XC.
- Füth, H.: 1902. Ueber Ovarialschwangerschaft. *Beitr. z. Geb. u. Gyn.*, VI.

- Freund, H. W., u. R. Thome: 1906. Eierstockschwangerschaft. Arch. f. path. Anat., CLXXXIII.
- Garrard, J. I.: 1916-17. A probable case of ovarian pregnancy. Jour. Med. Assn. Ga., VI.
- Giles, A. E., and C. Lockyer: 1914-15. Case of ovarian pregnancy. Proc. Roy. Soc. Med. Lond., VIII; Obst. and Gyn., Sect. 2-10.
- Gilford, Hastings: 1901. Ovarian pregnancy. Brit. Med. Jour., II.
- Idem*: 1899. Two further instances of extra-uterine (one tubal and one ovarian) gestation in which rupture occurred before the first month; operation. Lancet, I.
- Granville, A. B.: 1820. A case of a human fetus found in the ovarium of the size it usually acquires at the end of the fourth month. Philos. Trans. Roy. Soc. Lond., Pt. 1.
- Idem*: 1834. Graphic illustrations of abortion. J. Churchill, Lond.
- Grimsdale, T. B.: 1913. Case of ovarian pregnancy with full-time fetus. Jour. Obst. and Gyn. Brit. Emp., XXIII.
- Holland, E.: 1911. A case of ovarian pregnancy; probably bilateral. Jour. Obst. and Gyn. Brit. Emp., XX.
- Jaschke, R. T.: 1915. Ovarialgravidität mit wohlgehaltenem Embryo. Ztschr. f. Gebh. u. Gyn., LXXVIII.
- Jacobson, S. D.: 1908. True primary ovarian pregnancy; operation; recovery. Contributions to the Science of Medicine and Surgery, N. Y. Post-Grad. Med. Sch. and Hosp.
- Kantorowicz, Ludwig: 1904. Eierstocksschwangerschaft. Samml. klin. Vortr., Volkmann, N. F., Nr. 370, Gyn. 136, Leipzig.
- Kouwer, B. J.: 1897. Ein geval van ovarialzwangerschap (zwangerschap in ein Graafsch follikel) Nederl. Tijdschr. v. Verlosk. en Gynaec. Haarlem, VIII.
- Lea, S. W. W.: 1910. A case of ovarian pregnancy with diffuse intraperitoneal hemorrhage. Jour. Obst. and Gyn. Brit. Emp., XVIII.
- Leopold, G.: 1882. Ovarialschwangerschaft mit Lithopädonbildung von 35-jähriger Dauer. Arch. f. Gyn., XIX.
- Idem*: 1899. Beitrag zur Graviditas extrauterina. Arch. f. Gyn., LVIII.
- Lockyer, C.: 1916-17. Two cases of primary ovarian pregnancy, with a review of the literature 1910-1917. Proc. Roy. Soc. Med. Lond., X; Sec. Obst. and Gyn.
- Mall, F. P., and E. Cullen: 1913. An ovarian pregnancy located in the Graafian follicle. Surg., Gyn. and Obst., XVII.
- Mapes, Chas. C.: 1914. Ovarian gestation—being principally a review of the literature. Amer. Jour. Surg., XXVIII.
- Martin, R. S.: 1917-18. Three interesting cases. Va. Med. Semi-Monthly, XXII.
- Mills, H. M.: 1917. Probable ovarian pregnancy. Am. Jour. Obst., LXXVI.
- Meyer, A. W.: 1919. Uterine lysis, tubal and ovarian, and resorption of conceptuses. Biol. Bull., XXXIII.
- Norris, C. C.: 1909. Primary ovarian pregnancy and the report of a case combined with intra-uterine pregnancy. Surg., Gyn. and Obst., IX.
- Norris, C. C., and C. B. Mitchell: 1908. Primary ovarian pregnancy with report of a case. Surg., Gyn. and Obst., VI.
- Paucot, H., et A. Debeyre: 1913. Etude sur les grossesses ovariennes jeune. Ann. de Gynéc. et d'obst. 2s, t. 10.
- Roche, J.: 1902. De la grossesse ovarienne. Thèse de Lyon.
- Scott, N. S.: 1901. Ovarian pregnancy; is it an explanation of ovarian hematomas? Am. Med., II.
- Seedorff, M.: 1915. Ein Fall von geborstener Ovarialgravidität. Monatschr. f. Geb. u. Gyn., XLII.
- Sencert, L., et M. Aron: 1914. De l'indépendance qui existe entre le développement du placenta et celui de l'embryon (à propos d'un cas de grossesse ovarienne.) Bibliog. anat., t. 24.
- Spiegelberg, Otto: 1878. Zur Kasuistik der Ovarialschwangerschaft. Arch. f. Gyn., XIII.
- Sweeney, Thompson: 1917. Ovarian pregnancy. Med. Rec., XCII; Am. Jour. Obst., LXXVI.
- Tussenbroek, van, Catherine: 1899. Un cas de grossesse ovarienne (Grossesse dans un follicule de Graaf). Ann. de gyn. et d'obst., t. 52.
- The same*: 1899. Ovarialschwangerschaft (ein Fall von Schwangerschaft in einem Graafsch Follikel). Intern. Gynak. Kong. zu Amsterdam; Centralbl. f. Gyn., XXIII.
- Thompson, J. F.: 1902. Ovarian pregnancy, with report of a case. Trans. Am. Gyn. Soc., XXVII.
- Warbanoff, Peter: 1909. Ein Beitrag zur Graviditas ovarica. Inaug. Dissert., München.
- Webster, J. C.: 1904. Study of a specimen of ovarian pregnancy. Am. Jour. Obst., L.
- Webster, J. C.: 1907. A second specimen of ovarian pregnancy. Trans. Amer. Gyn. Soc., XXII.
- Werth, R.: 1887. Beiträge zur Anatomie und operativen Behandlung der Extrauterinen Schwangerschaft. Stuttgart.
- Werth, R.: 1901. Ovarialschwangerschaft. Handb. der Geb., von Winckel, Bd. II, Th. 2, Wiesbaden.
- Williams, J. W.: 1910. Ovarian pregnancy. Gynecology and abdominal surgery, Kelly-Noble, Phil. and Lond.
- Idem*: 1917. Obstetrics: A text-book for the use of students and practitioners, N. Y. and Lond.
- Young, E. B., and L. J. Rhea: 1911. Ovarian pregnancy. Report of a case. Bost. Med. and Surg. Jour., CLXIV.

GRANVILLE SHARP PATTISON¹

By WILLIAM SNOW MILLER, University of Wisconsin

Gross, in his biographical sketch of Pattison, says:

It is no exaggeration to say that no anatomical teacher of his day, either in Europe or in this country, enjoyed a higher reputation; his forte as a teacher consisted in his knowledge of visceral and surgical anatomy, and in the application of this knowledge to the diagnosis and treatment of diseases and of accidents, and to operations.

Being a man of intense feeling and strong prejudices he did not easily brook opposition. Because of these characteristics

the early years of his career were stormy and his reputation as a teacher was fully acquired only after many bitter controversies, one of which was so acrimonious that it was fought out on "the field of honor."

The year of Pattison's birth is usually given as 1791, but he says in his "Refutation," addressed to Dr. Nathaniel Chapman, of Philadelphia, under date of November 28, 1820, "I shall soon enter on the 28th year of my age"; this apparently makes 1793 the more correct date. He died November 12, 1852, after a short illness, of obstruction of the ductus communis choledochus.

¹ Read before The Johns Hopkins Hospital Historical Club, December 2, 1918.



GRANVILLE SHARP PATTISON.

Courtesy of Dr. J. M. H. Rowland.



NATHANIEL CHAPMAN.
Courtesy of Dr. Howard A. Kelly.

Granville Sharp Pattison was the youngest son of John Pattison, of Kelvin Grove, Glasgow. Of his early education we know nothing except the statement that he was probably educated at the University of Glasgow. That he was a hard-working student is shown by his being, when but 18 years old, assistant to Allen Burns, and on the death of Burns, in 1813, becoming his successor to the Chair of Anatomy, Physiology and Surgery in the Andersonian Institution, a recently organized medical school in Glasgow. Here he made quite a reputation as a lecturer, and had it not been for his naturally indolent nature and love of ease, would, no doubt, have attained in his later years preëminent reputation as an anatomist.

In November, 1818, charges were brought against him by Dr. Ure, one of his colleagues, of having committed adultery with his wife, and a divorce was obtained by Dr. Ure on that ground. The divorce laws of Scotland were at that time peculiar; all divorce procedures were brought in the consistory court, which was an ecclesiastical organization. It was not necessary that the parties charged with adultery had ever seen each other and the reputed paramour might not have ever existed. In any event, the accused paramour could not appear and defend himself. If the husband obtained a divorce from his wife on the ground of improper conduct, he could immediately bring a second action for damages and the accused party could then appear in court and endeavor to disprove the charge.

This second action was never instituted by Dr. Ure. After the arrival of Pattison in this country, Dr. Ure attempted to publish an octavo volume dealing with the case. One of his witnesses, however, having confessed that her declaration was false and that she had been induced to make her statements by means of threats and bribes, Dr. Ure suppressed the volume, for he could not sustain his charges, and had he attempted under these circumstances to circulate the publication he would have subjected himself to criminal prosecution. This episode was unfortunate for Pattison and it played an important rôle in the turbulent years which followed; for, although generally known to be unfounded, many years elapsed before it ceased to be recalled.

In Glasgow the charge was generally discredited, for Dr. Ure did not possess an enviable reputation; in fact, a statement is made that he barely escaped transportation to Botany Bay "for fraudulently stealing and destroying his father's will." In spite of this accusation Dr. Ure retained his position in the Andersonian Institution. Pattison explains the situation in the following statement:

The Andersonian Institution of which Dr. Ure is a member is an establishment of late date. The funds which were obtained for the erection of its buildings were procured by subscription; and as Dr. Ure was very active, at the time when the money was raised, in obtaining it, and granted to the subscriber of £20 a perpetual ticket of admission to one of the courses of his lectures, it has become a question, whether the money was bestowed on him as an individual, he granting personally an equivalent, or to the Corporation of the Institution.

When Dr. Ure, about six years ago, fraudulently stole his father's will for the purpose of defrauding his family, an attempt was made

to expell him from the institution; but as the Trustees, upon taking advice, learnt that his expulsion would involve them in a tedious litigation, a litigation which would require to be carried on by money advanced by them as individuals, the attempt was abandoned.

Replying to this, Dr. Chapman shows that the institution was incorporated on June 9, 1796; when the buildings were ready for occupation he does not state, but he does infer that Pattison was guilty of a misstatement in that he considered an institution 21 years old as an "establishment of late date." The founder of this Institution was John Anderson, a Scottish naturalist, who in his will provided for its establishment; he died January 13, 1796, and the incorporation on June 9, 1796, was undoubtedly the first step in carrying out the provisions of the will. The medical department gave its first courses in 1799.

Dr. Chapman attempts to offset the statement in regard to the will of Dr. Ure's father by saying:

Not long before he came to this country, Mr. Pattison was tried for a felony, in stealing a body from the grave. . . . Mr. Pattison merely escaped from want of evidence that he had taken the clothes of the deceased; the part of the offence most penal under the Scotch law.

In this instance Pattison was in the best of company, for John Hunter, Sir Astley Cooper and nearly every teacher of anatomy up to the passage of the "Anatomy Act" in 1832, might with more or less justice be termed an "acquitted felon."

The occasion of Pattison's coming to Philadelphia was the expectation of occupying the Chair of Anatomy in the Medical Department of the University of Pennsylvania, made vacant by the death of Professor Dorsey and temporarily filled by Prof. Philip Syng Physick. That he was given to understand before leaving England that the position was open to him is certain, but that this was unofficial is also certain.

On December 24, 1818, Pattison received a letter from his brother, John Pattison, who at that time resided in Philadelphia, in which he states that his legal adviser, Mr. Chauncy, agreed with him that there was an opportunity for a man of talent to be appointed to the position left vacant by the death of Dr. Dorsey. The fact that he was a foreigner was certainly against him, but he was "inclined to think that the trustees will be more guided by talent, than by any other consideration." He advised that letters be obtained from Astley Cooper and others and "you had better say the extent of your museum, etc., which I know Mr. Burns considered invaluable."

Under date of April 20, 1819, Dr. Dewees, of Philadelphia, wrote Pattison a letter which contained the following statement:

I have, contrary to any right, taken the liberty to advise upon the subject. As far then as a firm belief that you would succeed (and that belief founded on pretty certain data) will offer an inducement to pay us a visit, I have no hesitation to declare, that no question remains in my mind, that were you on the spot, your election would be certain. It is unquestionably the opinion of two of the most influential and best informed men here. Your visit should be as prompt as possible, that you might have the necessary time for the preparatory arrangements here. My opportunities

to judge of the sentiments of those, who have this gift in their power, will be best explained by your brother.

Acting on this advice Pattison arranged his affairs as quickly as possible and sailed from Liverpool for New York, where he landed July 6, and on the evening of July 7, 1819, reached Philadelphia.

The two "most influential and best-informed men" referred to above were Drs. Chapman and Physick. Each of these denied having authorized the use of his name. Chapman states:

The trustees, after postponing the appointment for six months . . . had publicly advertised that they would receive applications from any quarter. But we soon discovered our mistake—for at their first meeting which took place not many days afterwards, when all the testimonials of Mr. Pattison were submitted to them, so far from a favorable impression being made, these recommendations were treated contemptuously, as extravagant and hyperbolic—it being quite manifest, that no individual with half the merit which they set forth, would sacrifice his actual possessions, to embark in so adventurous a scheme!

Chapman evidently forgot that Philadelphia and the country in general was peopled with those who had left the old country and settled in this country because they thought that they had here an opportunity to improve their condition—that they were adventurers.

Shortly before sailing, while he was in London, Pattison was made a member of the Medico-Chirurgical Society of London and a Fellow of the Royal College of Surgeons. Had there been the stain on his character which was charged against him, it seems doubtful if these honors would have been bestowed on him. The "testimonials" were written by Prof. John Barclay and Dr. Thompson, of Edinburgh; Francis Jeffrey, editor of the *Edinburgh Review*; James Wardrop and Astley Cooper, of London; the Rev. Dr. Love, of Glasgow, a celebrated clergyman of the Kirk of Scotland; Sir James McGregor; Sir William Adams; and others.

Just at this time there was a good deal of intrigue taking place in the faculty of the University of Pennsylvania, and in 1819 Philip Syng Physick,

Yielding up his own better judgment to the schemes of others, for perhaps the first time in his life, allowed himself to be transferred—for the act was not of his own choice—from the chair of Surgery, to that of Anatomy, from the place where he was emphatically *at home*, to one in which he was *comparatively a stranger*.

Pattison did not accept any appointment in the University, though one was offered to him; he also declined a professorship in the Transylvania University at Lexington, Ky. Chapman makes Pattison's declination of the call to Lexington appear in a false light and says:

The College, were, moreover, as I am told, justly indignant at the disrespectful manner in which they were treated, considering the only motive of Mr. Pattison, in procuring the appointment, was to have it published as an early recognition of his consequence in this country.

He also states that Dr. Caldwell was furnished with all of Pattison's documents, and had a distinct understanding with

Pattison that if he were elected he would accept. If such were the case, Dr. Caldwell would not fail to make mention of it in his "Autobiography," for such episodes as this are favorite themes in his narrative. A careful reading of Peter's "History of the Medical Department of Transylvania University" also fails to reveal a single reference to this incident.

In 1820 Pattison was elected Professor of Surgery in the University of Maryland, and he looked forward to leaving behind him all the intrigue and malevolence he had encountered at Philadelphia, fostered in a large degree by Dr. Nathaniel Chapman. This did not materialize, for One of the faculty, a Professor in the University of Pennsylvania! came to Baltimore immediately after my settlement in that City, apparently for the purpose of shutting me out from the hospitality of the citizens, by the most foul, the most malignant, the most false aspersions against my character.

The animosity existing between Pattison and Dr. Chapman, who seems to have been the moving spirit in the campaign against Pattison, soon reached an acute stage and Pattison issued a challenge to Dr. Chapman, which he did not accept. This led Pattison to go to Philadelphia, and on October 23, 1820, he put up in two public places the following post:

TO THE PUBLIC

Whereas Nathaniel Chapman, M. D., Professor of the Theory and Practice of Medicine in the University of Pennsylvania, etc. etc. has propagated scandalous and unfounded reports against my character; and Whereas when properly applied to, he has refused to give any explanation of his conduct, or the satisfaction which every gentleman has a right to demand, and which no one having any claim to that character can refuse, I am therefore compelled to the only step left me, and Post the said Dr. Nathaniel Chapman, as a liar, a coward and a scoundrel.

GRANVILLE SHARP PATTISON.

Following the European custom Pattison resolved to stay two days in Philadelphia; but, he says:

My stay, however, was not long, left to my option. . . . I was arrested at 11 o'clock A. M. of the day on which I had put up the post. Dr. Chapman denies all agency in the matter, be it so.

When the case came before the grand jury, all the correspondence in the case was furnished by Chapman, and Pattison says:

Perhaps he did this that I might be convicted, in order that an opportunity might be furnished him of displaying his *generosity* and magnanimity, by applying "instantly in person to the Executive" for my "pardon."

In his letter refusing to meet Pattison, Chapman gives as his reason, "the character and conduct of Mr. Pattison, as well in relation to the causes which compelled him to leave Scotland, as to events which have subsequently happened." Not satisfied with this, in November, 1820, Chapman issued a pamphlet in which he attempts to justify his conduct. To this Pattison replied in a like manner November 28, 1820. Pattison "had the good fortune and address to enlist the sympathy of his colleagues and a large part of the community in Baltimore in his behalf, and presenting his side of the case to a committee of prominent citizens, he was exonerated from all blame."

This was not Chapman's first "affair": he had some years before challenged Dr. Dewees. In regard to this affair Chapman says:

It happened fifteen or sixteen years ago; and if my conduct was reprehensible, I hope I have since atoned for it, by a friendship warm, cordial and sincere. What, however, will be thought of the malignity of a man, who thus endeavors to disturb the happiness of families, by references of this nature!!

Pattison replying to this does not put Chapman in an enviable light:

I have not a "numerous family," I admit, and here I allow there is a distinction. But did Dr. Chapman before he had a family, when he challenged Dr. Dewees, who had a numerous one, think this excused him?

The quarrel between Chapman and Pattison was finally taken up by General Thomas Cadwalader, Dr. Chapman's brother-in-law, and four years after Pattison's arrival in this country (1823?) they met somewhere in Delaware. Cadwalader received the ball from Pattison's pistol in his "pistol arm" which was disabled thereby during the remainder of his life. Pattison was uninjured, "but a ball passed through the skirt of his coat near the waist."

In 1826 Pattison resigned his professorship at Baltimore and returned to England. Why he resigned a position which with his professional services he states was bringing him \$10,000 a year is not clear; for, as a teacher, he had a successful record while in Baltimore, and the University of Maryland enjoyed its greatest prosperity. On the one hand, is the statement that he "led a very gay life" in Baltimore and that his health was thereby impaired and that after he left it was doubtful whether he recovered; on the other hand, there is Pattison's flat denial and 26 additional years of active life.

In July, 1827, Pattison was appointed Professor of Anatomy in the newly organized University of London. Before long he became involved in difficulties, different from those at Philadelphia, but equally disastrous. Pattison was a Scotchman and had taught in Scotland and "America"; he had introduced as a text-book Fyfe's anatomy, written by a Scotchman; he had for his demonstrator a Mr. Bennett, an Englishman, who had conducted a school of anatomy in Paris which had, very properly, been refused credit at an English institution; he had incurred the displeasure of Wakley, editor of the *Lancet*, who supported Bennett; but chief of all he was a Scotchman. If any one doubts the attitude of London at this time towards Scotchmen let him read Pichot's "Life and Labors of Sir Charles Bell" and the "Letters of Sir Charles Bell" by his brother George.

Wakley began his attack on Pattison by a sharp criticism of Fyfe's anatomy; it must be acknowledged, however, that the criticism was justified. Wakley was a friend of the medical students and supported them in most of their complaints and, possibly, prompted some of them. That he was responsible for many reforms in medical instruction and medical practices is to his credit, and he deserves all the credit accorded to him, but he sometimes overshot his mark; take, for example, his

attitude towards Sir Charles Bell, Marshall Hall, and others who have left an honored name and life work.

On July 23, 1831, Pattison was dismissed from the Chair of Anatomy at the University of London. The events preceding and following his dismissal are full of interest. Clarke, in his "Autobiographical Recollections of the Medical Profession," says:

No matter what a man's talents and acquirements might be, he had little or no chance of advancement at a Hospital, except through family or money influence. All the prizes in the Profession were monopolized by those who could pay for them, or who were fortunate enough to have friends at Court. The apprentice of the Hospital Surgeon paid a very large premium for his indentures, and, as a rule, it was understood, that he was to be placed on the Hospital staff as part return for his money outlay. This gave rise to a system of nepotism of the most objectionable character: Hospital Surgeons were selected, not from the mass of the Profession, but from the private pupils and relations of the "staff." . . .

To add to the discontent prevailing, there had been (1827) an unseemly quarrel at the great Hospital of St. Bartholomew's, in which Mr. Abernethy did not bear an enviable part. . . . At this time, too, the establishment of what was then called the "University of London" attracted increased attention to the system of nepotism. . . . The announcement of the names of Professors of this Institution startled the Profession by the fact that most, if not all but one of them, were "outsiders"; were not, in fact, connected with any of the large endowed Hospitals, but were all of high and deserved distinction.

The first name on the list given by Clarke is that of Pattison.

In the issue of the *Lancet* for March 5, 1831, there is a communication signed "A Senior Student of the London University" in which an attempt is made to show that Pattison is unworthy of his professorship and that Bennett should have the position. Much of "Senior Student's" complaint and most of the student dissatisfaction is based on the fact that Pattison attempted to enforce discipline in his classroom. That Wakley had previous knowledge of what was taking place in Pattison's lecture room is shown by the following quotation from the above-mentioned communication:

You are already, Sir, aware of the proceedings which were instituted during the last session by a part of the medical students against one of the lecturers upon anatomy, Mr. Pattison.

This communication was replied to by another student, who signs himself "Veritas," under date of March 7, 1831, and throws considerable light on the case. One of the charges brought against Pattison in the original complaint was "that the defect in his articulation rendered him unfit for the chair." This charge was afterwards erased. It is interesting to note that this is identically the same charge brought by Wakley against Sir Charles Bell. "Veritas" says "a more unkind and unfeeling imputation could not have been made." Toward the close of his reply "Veritas" says:

Picture to yourself, Sir, an assembly of mere youths, many of whom have just commenced their studies, met together to decide upon the ability or inability of a professor who was engaged in teaching anatomy before many of them had an existence. The very idea is preposterous.

He goes on to say that he has attended two sessions of Pattison's lectures and has always found them instructive and any one who pays attention to his lectures "cannot fail of reaping abundant store of anatomical knowledge."

As stated above, Pattison was dismissed July 23, 1831. The resolutions passed by the Council show that they finally yielded to the student clamor; but

In taking this step the Council feel it due to Professor Pattison to state, that nothing which has come to their knowledge, with respect to his conduct, has in any way tended to impeach either his general character, or professional skill and knowledge.

One member of the Council protested vigorously, but vainly, against Pattison's dismissal and enumerates eight reasons why he should not have been dismissed. In the seventh item the statement is made that the other professors testified to the excellency of Pattison's qualifications and that "many of them had expressed their firm conviction to the Council, that the dissensions in the medical school did not arise out of any defect or misconduct of Professor Pattison." They evidently had in mind outside influences.

From this time until the end of the controversy in the *Lancet* the discussion was confined mainly to Wakley and Pattison, with now and then short communications from some of Wakley's friends. The final shot was fired by Pattison and his closing paragraph is exceedingly interesting reading:

In the letters of Drs. Turner and Thompson, and in your "strictures" on my Statement, the fact of my having been a successful teacher in the United States is treated with great contempt. "It does not follow," observes Dr. Turner, "that he could succeed in London because he was successful in America." The Americans, forsooth, are easily satisfied. It is very well for John Bull to say so. I should, however, have expected that you were too well informed as to the state of medical science in the United States, to have given currency to such a vulgar and unfounded prejudice. The Americans, I assert, are as far advanced and as enlightened in their medical opinions as any country in Europe; and I would further assert, without the fear of contradiction, that there may be numbered amongst the medical profession of that country, gentlemen who, for extent and profundity of knowledge, and for capacity of conveying instruction, have no reason to fear comparison with the most eminent teachers in Europe. Let the improvements in medical and chirurgical science be reviewed for the last thirty years, and it will be found that America has furnished her full quota.

This defence of American medicine and American medical men by one who had good reason for resentment shows Pattison to have been a man of more character than is generally acknowledged.

Shortly before Pattison was dismissed from the Chair of Anatomy Bennett died and the Committee of Education of the University of London looked about for a new professor. They were fortunate in their selection, for they recommended Mr. Jonas Quain for the professorship and his brother, Mr. Richard Quain, for demonstrator, and peace reigned for the time being.

Pattison was not long without a professorship, for in 1832 he took up his duties as Professor of Anatomy in the Jefferson Medical College, in Philadelphia, where he met with immediate success. He held advanced ideas as to the best way in

which anatomy should be studied, as the following abstract from the annual announcement of the Jefferson Medical College for the year 1832 shows:

Anatomy, the basis of all medical reasoning, can only be studied *practically* during the term of the student's attendance on lectures. Should he neglect his opportunities for acquiring a complete knowledge of the science during the term passed by him at college, he must be content to continue forever afterwards a mere driveller in his profession. Now, anatomy is not to be learnt by an attendance on lectures. Dissection, and dissection alone, can make a man an anatomist. The Professor of Anatomy, it is true, may, by animated and masterly demonstrations, do much to guide and assist the anatomical student in true prosecution of his studies, but it is in the dissecting room, with the dead body before him, by patient and assiduous dissections, that the student can alone acquire a knowledge of anatomy.

Pattison remained in Philadelphia until 1841, when he joined in founding the Medical Department of the University of New York. Here he held for the remainder of his life the Professorship of General Descriptive and Surgical Anatomy.

With his return to this country, the strife and turmoil of his life very largely disappeared. He married a Scotch lady by the name of Sharp, who was possessed of some fortune. I have been unable to ascertain the date of their marriage, but it proved to be a very happy one, for Gross gives a pleasing picture of their domestic life. He was social, ever ready to do a kind act, a lover of the beautiful in nature and art. He took an active interest in establishing the Grand Opera House in New York. He also was an enthusiastic disciple of Izaak Walton.

Pattison was the author of "The Register and Library of Medical and Chirurgical Science." He edited with notes Burns' Surgical Anatomy of the Arteries of the Head and Neck, Masse's Anatomical Atlas, and Cruveilhier's Anatomy; he was one of the editors of the *American Medical Recorder*, a journal which contains many of his contributions to medical literature.

NOTES

Pattison's Exoneration.—All the facts concerning the divorce obtained by Dr. Ure were laid before the managers of the Andersonian Institution by James Burn, "Writer of the Signet," and Pattison was completely exonerated by them.

Pattison's Museum.—Cordell states that this "was extensively advertised in the medical journals and newspapers of the country." After he went to the University of Maryland he exerted a considerable influence in the councils of the University and he eventually induced the University to purchase it for \$8000, and in 1821 a new building (Practice Hall) was erected for its accommodation. It consisted "of upwards of 1000 selected morbid and healthy specimens, and in variety, excellence and number was far superior to any other in America." For some time it constituted the chief attraction for visitors to the University. Many of the preparations are still extant, but in a somewhat neglected condition.

Dr. Physick's Transfer to Anatomy.—Chapman made the statement to Pattison that he thought by transferring Dr. Physick to the Chair of Anatomy and by bringing Dr. Gibson from Baltimore to occupy the Chair of Surgery the changes "would operate beneficially in two ways. It would strengthen the University of Pennsylvania, and at the same time weaken that of Maryland." This was before Pattison received his call to Baltimore.

Position Offered at the University of Pennsylvania.—The position offered Pattison at the University of Pennsylvania was to be shared with another, and he did not care to accept such an arrangement. He therefore began to give independent lectures on anatomy and surgery and he says that he had "a class of above one hundred and ninety students." The hour of Pattison's lecture was fixed after consultation with Chapman and was one which Chapman assured Pattison would not conflict with any of the professors. When, however, Chapman learned that Pattison's lectures were popular with the students he changed the hour of his own lecture to that used by Pattison and thus prevented the students from attending Pattison's lecture.

Gibson-Pattison Controversy.—Apparently no one in Philadelphia knew of the particular structure demonstrated by Pattison. Gibson, however, found in Colles' Surgical Anatomy "an unusually full and well-written account of those very parts, which Mr. Pattison had claimed as a discovery of his own." Like many another worker Pattison thought he had found something new, but as soon as he found he had been anticipated he withdrew all claims of discovery, only claiming that certain post-operative results were best explained by the presence of this structure (Colles' fascia).

Gibson's Characteristics.—"He was very vain in his personal appearance, and more so of his reputation as a surgeon and teacher of surgery. His style of lecturing was easy, agreeable, and instructive, but he never omitted an opportunity to set forth his own merits and to depreciate the ability of surgeons whom he disliked. He was especially vindictive against his leading rival in Philadelphia." In 1847 Gibson was in Europe and returned late in the fall with a wardrobe of broadly striped waistcoats and trousers to match. These he displayed to his class until the lot was exhausted, causing much merriment in the class-room and prolonged rounds of applause which he received as evidence of his personal popularity (Busey, U. P., 1848). Dr. S. D. Gross says, "Gibson was not an amiable man. His ill temper often betrayed him into unkind expressions, even in the lecture room."

During his last illness Gibson sent for Gross. "My acquaintance with him was slight, and I was therefore not a little surprised when I received a message to visit him at his country residence. An old friend, to whom I mentioned the fact, exclaimed, 'Don't you know that he has no friends in the medical profession of Philadelphia.'"

Pattison's Brogue.—"What added interest to the speaker was a slight lisp and a Scotch accent, which never entirely forsook him, despite his efforts to overcome them in early life" (Gross).

Chapman as a Teacher.—"A cleft palate, with its consequent indistinct utterance, robbed him of every charm as a teacher, for which his vast experience, great learning, and qualities of heart and mind so well fitted him. The most careful attention, near and in front of him was necessary to catch the words as they were spoken, except by those who by long experience had become accustomed to his unfortunate and defective enunciation" (Busey, U. P., 1848).

He (Chapman) "has seen several cases of hydrocephalus in girls about the age of puberty, caused by metastasis of action from the uterus to the brain."

Chapman believes "many cases that have a decided character of angina pectoris afterwards terminated in well-marked gout cases. A gentleman long afflicted with this affection had gout induced in his extremities by the use of sinapisms, and the former affection was relieved; but, improperly removing the sinapisms, the disease suddenly returned to its place and immediately killed him."

Epilepsy, "usually assigned to a certain state of the nervous system—a peculiar sensibility or irritability—it is the temperament of genius and intellect—Julius Cæsar, Mahomet, Napoleon, etc." (From bound volume of MS. notes taken by James C. Hall (U. P., 1827) of Chapman's lectures delivered in 1826.)

Pattison's Resignation from the University of Maryland.—Pattison, in his "Statement of Facts in his connection with the University of London," says that it was his intention to return to the States and deliver another course of lectures; instead of doing this he spent some time in Germany. I have tried to ascertain the date of his resignation, but have been unsuccessful. This might help by showing that he resigned from the University of Maryland to accept the position in the University of London.

Pattison's Resignation from the University of London.—The only medical man who was a member of the Council of the University of London (Dr. Birkbeck) supported Pattison and opposed Mr. Bennett and the way in which Bennett was appointed. I do not think that Pattison, at the time he wrote his "Statement of Facts," realized the extent of Wakley's opposition and influence. Later he understood it better and gave it proper consideration.

Defense of American Medicine.—Medicine in the United States 1800 to 1830. Pattison, in the closing paragraph of his final communication made the statement that if the advances in medicine and surgery "be reviewed for the last thirty years, it will be found that America has furnished her full quota." I have had the curiosity to look up American medicine during this period and find abundant material to substantiate his affirmation.

In Boston, there was John Warren and J. C. Warren, eminent as anatomists and surgeons—the latter founder of the Massachusetts General Hospital; James Jackson in internal medicine and Jacob Bigelow, who published in 1829 his "American Medical Botany"—his essay "On Self-Limited Diseases" did not appear until 1835. In New York, Wright Post and Valentine Mott were doing pioneer work in surgery. In Philadelphia, there was Casper Wistar and W. E. Horner in anatomy; Philip Syng Physick in surgery; John C. Otto in clinical medicine (he was the first to describe hemophilia); J. K. Mitchell in neurology; W. P. Dewees in obstetrics; Nathaniel Chapman in the theory and practice of medicine. In Connecticut, Elisha North was introducing vaccination, recommending the use of the thermometer in fevers and in 1817 established the first eye infirmary in the United States.

Nathan Smith was establishing medical schools in New England and furnishing the entire faculty; he was a pioneer operator for ovariectomy and, in 1824, published his essay on "Typhus Fever," now a medical classic.

In the West there were four men who have made a name in American medicine, Ephraim McDowell, B. W. Dudley, William Beaumont and Daniel Drake. McDowell is known the world over as the father of ovariectomy (Nathan Smith did not know of his operation when he operated in 1821). Dudley was famous in his day for his success in lithotomy. Beaumont, in 1825, began those studies on digestion which he gave to the world in 1833. Drake was establishing medical schools and publishing essays on medical education in the *Western Journal of the Medical and Physical Sciences*; at the same time he was preparing for his great work, "Diseases of the Interior Valley of North America."

Other names could be added to this list, but it is unnecessary. I consider the point raised by Pattison well proven.

Has the Faculty of the University of Maryland Accepted?—The Professor of Surgery at the University of Pennsylvania (Dr. Gibson) in a clinic at the Philadelphia Alms House, open to students of the Jefferson and the University, referred slightly to the claim of the Professor of Surgery at Jefferson (Dr. McClellan) that he had performed the operation (under a general attack on Sir Charles Bell who had made the same claim). He refers to Bell as a *Cambrachian*, such more worthy of his gun than the *Dapper* (Dr. McClellan).

Pattison took up the challenge and made a reply which was brilliant for its wit and sentiment and convincing with its weight of learning. In the same publication Pattison ridicules the story that he was so ignorant of the subject that he mistook the omohyoid muscle for the carotid artery and was about to ligate it

when one of his students called his attention to the mistake and being set right by his pupil, found the artery and tied it.

I have tried unsuccessfully to ascertain what were the relations between Chapman and Pattison after his return to Philadelphia as Professor of Anatomy at Jefferson. Dr. J. W. Holland, of Philadelphia, made inquiries for me of a distant relative of Dr. Chapman and reported that "he does not know a living soul who could state what were Chapman's relations to Pattison in later years." As nothing further appears in print, the animosities of earlier years seem to have died out and disappeared.

BIBLIOGRAPHY

- Bell, John: Philip Syng Physick. Philadelphia, 1861.
 Busey, Samuel C.: Personal reminiscences and recollections. Washington, 1895.
 Chapman, Nathaniel: Correspondence between Mr. Granville Sharp Pattison and Dr. N. Chapman. Philadelphia, 1820.
Idem: Case of divorce of Andrew Ure, M. D., vs. Catherine Ure Philadelphia, 1821.
Idem: Correspondence between Mr. Granville Sharp Pattison and Dr. N. Chapman. 2d edition, with explanatory remarks. Philadelphia, 1821.
 Clark, J. F.: Autobiographical recollections of the medical profession. London, 1874.
 Cordell, E. F.: Historical sketch of the University of Maryland School of Medicine. Baltimore, 1891.

Gibson, William: Strictures on Mr. Pattison's reply to certain oral and written criticisms. Philadelphia, 1820.

Gross, Samuel D.: Autobiography, 2 vols. Philadelphia, 1887.

Henry, F. P.: History of medicine in Philadelphia. Philadelphia, 1897.

Lancet, The: London, 1830-31, 1831-32.

Pattison, G. S.: Experimental observations on the operation of lithotomy, with the description of a fascia of the prostate gland, which appears to explain anatomically the cause of urinal infiltrations and consequent death. Am. Med. Recorder, 1820, III.

Idem: An answer to a pamphlet entitled "Strictures on Mr. Pattison's reply to certain oral and written criticisms, by W. Gibson, M. D." Philadelphia, 1820.

Idem: A refutation of certain Calumnies published in a pamphlet, entitled Correspondence between Mr. Granville Sharp Pattison and Dr. Nathaniel Chapman. Baltimore, 1820.

Idem: Final reply to the numerous slanders circulated by Nathaniel Chapman, M. D., Professor of the Institutes and Practice of Medicine in the University of Pennsylvania. Baltimore, 1821.

Idem: Professor Pattison's statement of the facts of his connection with the University of London. London, 1831.

Idem: A lecture delivered in Jefferson Medical College, Philadelphia, on the evening of Tuesday, the 22d of January, 1833, on the question "Has the parotid gland ever been extirpated?" Published by the students of Jefferson Medical College. Philadelphia, 1833.

COMMENTS ON THE PATHOLOGY AND BACTERIOLOGY OF FATAL INFLUENZA CASES, AS OBSERVED AT CAMP DEVENS, MASS.

By S. BURT WOLBACH, Boston

Death from influenza means death from lung complications—pneumonia in some form. The pathological picture of the lungs as seen in a series of postmortems is a kaleidoscopic one. At first it was most difficult to correlate the various gross findings, and it also has been difficult to correlate the microscopic findings, and this part of the work is not yet completed. I have had the advantage of comparing my observations with those of Dr. Goodpasture at the Naval Hospital at Chelsea, Mass., and again with a study of the series of cases we have had at the Peter Bent Brigham Hospital in Boston, and it now is possible to give a fair account of the probable sequence of events and to explain the apparent great differences in the pathology.

In a series such as is presented here two types of lungs stand out as strikingly characteristic findings in this disease. The first is encountered in those cases in which death has occurred within a few days after the onset of pulmonary signs. These cases yield lungs which are partially collapsed, dark red, lax, but meaty in consistency. The pleural surfaces are often partly covered with a dusky red mottling, due to small extravasations of blood beneath the serous coat. There may be a thin layer of dusky red fibrinous exudate upon the pleural surfaces, particularly over the posterior borders. On section these lungs are dark red and wet. They are dripping wet, and the fluid from some portions is a blood-tinged serous liquid and from others dark red and bloody. On close inspection the cut surfaces are usually found to be thickly sprinkled with air

vesicles of considerable size. The lung tissue as a whole, after the liquid has drained from it, is brownish-red in color, and somewhat translucent and friable. The mucosa of the bronchi is usually very dark red in color, and the bronchial lymph nodes are enlarged and deep red in color.

The other type of lung, which is found in patients that have lived for 10 days or more after the onset of the disease, while showing traces of the type of lesion just described, is characterized by a very extensive bronchitis, with broncho-pneumonia, discrete or confluent, and peri-bronchitis. These lungs are more voluminous than the preceding, but they do not fill the chest cavity at postmortem. They are nodular, and the pleural surfaces occasionally show a striking tracery, due to the injection of the sub-pleural lymphatics. Portions of the surfaces of the lungs may be covered with a thin layer of fibrinous exudate. On section the most prominent feature is the extensive injection of the bronchi, particularly the smaller ones, with a fibrino-purulent exudate. The injection of the bronchi may be so extensive and uniform as to produce geometrical patterns, which are very striking when the condition is accompanied, as it usually is, by a marked infiltration of the inter-lobular septa. A casual inspection suffices to show that the smaller bronchi are distended, usually markedly dilated, and in cases of two weeks' duration spherical and cylindrical bronchiectases are very common. The gross appearances of this type of lung are very much like those described by Dr. MacCallum in pneumonias after measles. The condition in fact

is one of pan-bronchitis; peri-bronchitis with extensive infiltration of the interlobular septa; and organization in alveoli and bronchioles.

These two predominating types on first consideration seem to represent different processes. I hope to show convincingly that they simply represent different stages of the same process. Before I undertook the study of the Camp Devens cases I had some experience with influenza pneumonias at the Peter Bent Brigham Hospital, and I have since quickly surveyed the material obtained there during the time I was at Camp Devens. The Brigham Hospital cases, on the whole, have been quite different in their gross appearances. On the other hand, the cases at the Naval Hospital in Chelsea have been very similar to those at Camp Devens, and I think a cross-section of the study of one series of cases is very much like that of the other—to which Dr. Goodpasture agrees. There are many other interesting features of the pathology of the lungs, such as the rapidity with which bronchiectasis occurs and the large number of cases which develop interstitial emphysema, and of course the consequences of both of these conditions; bronchiectatic abscesses and gangrene of lungs from the first, emphysema of the mediastinum and subcutaneous emphysema from the second. Of this series of 28 postmortems, done between the 2d and 32d day of the disease, there were six that showed subcutaneous emphysema; eleven showed emphysema of the mediastinum.

In comparing notes with other pathologists one is struck by the differences in gross appearances of the lungs in different localities. The same is true in regard to the bacteriology. The table which accompanies this report shows the very high percentage of pure *Bacillus influenzae* pneumonias at Camp Devens; again, a similarity with the series at the Chelsea Naval Hospital as reported by Keegan. However, in the Camp Devens series there were a few cases in which the hemolytic streptococcus and the pneumococcus were found, and these lungs presented different gross appearances. In a cursory analysis of the Brigham Hospital cases autopsied (about 30), I find a predominance of hemolytic streptococcus and pneumococcus lungs. Without going into corroborative details at this time, I may say that in the gross appearance of the lungs I have laid emphasis upon *B. influenzae* was the only organism which could be cultivated and I unhesitatingly associate these distinctive conditions with that organism. In lungs showing other types of solidification, other organisms were responsible for the exudation characterizing the pneumonias. The hemolytic streptococcus, the staphylococcus and the pneumococcus, each produces its distinctive picture, the last often that of lobar pneumonia.

While the bacteriological evidence, based upon the assumption that *B. influenzae* is the cause of influenza, is in good support of the stand that there is a distinctive lung lesion in these influenza pneumonias, the histological study has afforded very definite proof. Early in this study of the Camp Devens cases, I recognized the fact, as have others, that a striking type of reaction was present, a condition of acute alveolar emphysema with the deposit of a hyaline fibrinous material on the alveolar walls. The intervening alveoli are

compressed and filled with exudate, which in the early cases is largely serous or bloody, containing but little fibrin. It is this acute alveolar emphysema, with the serous and hemorrhagic exudate, that gives the characteristic gross appearance to the lungs in the early stage of the disease. In order to determine how common this lesion is, I have gone over all of the Brigham Hospital autopsies on influenza cases, and find it to be constant. It may be masked by a pneumococcus or streptococcus exudation or by extensive hemorrhage, but its presence can always be determined by the finding of the hyaline fibrin outlining greatly distended air spaces in the lungs. It is the one distinctive feature in the pathology of influenza pneumonias, and its constant occurrence is indicative of the entity of the initial lung infection. The interpretation of this lesion was not easy. The hyaline fibrin, because of its prominence and the juxtaposition of cellular exudate, often simulates the outlines of alveoli. As a matter of fact, it outlines cavities filled with air, which may or may not completely fill groups of alveoli. Although alveolar walls in contact with this fibrin may be necrotic, tissue elements play no part in its formation. A similar hyaline fibrin was found in two cases of emphysema of the mediastinum where the mediastinal areolar tissues were infected by pneumococcus, secondary to pneumococcus pericarditis. The physical characteristics of this fibrin are determined by its contact with air, and an important factor is probably the mechanical compression of strands of fibrin by air. What is the source of the exudation in the alveoli in these early pneumonias? The exudation may be present in alveoli with intact walls, or walls showing very slight reaction, mainly evidenced by activity of the respiratory epithelium. In all cases severe lesions were found in the finest bronchioles, and in the alveolar ducts. The latter show an exudation composed mainly of polymorphonuclear leucocytes and small quantities of fibrin. The walls are filled with leucocytes, and are often necrotic in places. The intralobular bronchioles show severe lesions of the mucosa, and it is often possible to demonstrate the source of hemorrhages from capillaries. The obvious explanation, and indeed the only possible one from the material at hand, is that the major injury is to the bronchial system, and mainly in the finest bronchioles and alveolar ducts. To secure the degree of emphysema present it is necessary to assume a valve action of the exudate in the bronchi. The character of the hyaline fibrin deposit around air vesicles and upon the alveolar walls suggests a pouring of exudation into the alveoli from the bronchioles and alveolar ducts, at a time when air is able to pass. Thus the patient is virtually blowing bubbles in his own lungs, into a medium of exudation relatively poor in fibrin.

The mechanism of interstitial emphysema formation is easily seen, where the greatly distended alveoli are in contact with the pleura of interlobular septa. In these locations it is possible to demonstrate rupture of the alveolar walls and the direct continuity of fibrinous strands, partially filling clefts dissected by the air from alveoli to pleural or interlobular connective tissue. A series of gross sections and microscopic sections from lungs with interstitial emphysema shows that the air finds the easiest route of exit from the lung in the con-

nective tissue surrounding blood-vessels. It dissects along blood-vessels to the hylus of the lung and from there along the great vessels and bronchi into the mediastinum, over the pericardium into the anterior mediastinum, and upwards along the trachea into the tissues of the neck, whence it escapes into the subcutaneous tissues. This subcutaneous emphysema may appear very early, as will be seen by the accompanying chart. The earliest case was seven days from the first symptom, which means, of course, a shorter duration of the lung involvement. The majority of the cases were noted on or after the 10th day from the initial symptoms of the disease.

It must be borne in mind in considering the pathology of these lungs, that the lesions are not uniformly distributed, and therefore very extensive injury in portions of one or several lobes are compatible with life for a considerable period of time. The bronchial lesions apparently progress, and may extend throughout the whole of one or both lungs, producing the anatomical picture of the more chronic cases, that of a pan-bronchitis with bronchiectases and peri-bronchitis. During this period of extension in bronchi, a number of things may happen to the portions of the lungs first involved. They may become secondarily infected with pneumococcus or streptococcus, or the Gram-negative diplococcus called by English workers "Diplococcus mucosus." In rare instances Staphylococcus and Friedlander's bacillus have been encountered. The fate of the tissue depends on the nature of the infecting organism; as, for example, fibrinous exudation with the pneumococcus and abscess formation with the staphylococcus. In a number of instances these portions of the lungs, severely damaged at the onset, did not become secondarily infected; at least, these lungs have shown only the influenza bacillus at the autopsy, and have undergone extensive organization resulting in cicatrices of large sizes. If we take a series of lungs which have shown only the influenza bacillus in cultures and in sections, we may still have all the stages described exclusive of those with secondary infection, and accordingly we must conclude that the reaction to the influenza bacillus is less intense in the later stages of lung involvement than in the earlier. This is shown best in comparing two lungs from the same case, where in one lung, usually the right, we find the severe damage of the early lesion with bronchiectasis and peri-bronchitis, and in the other lung a much less intense bronchial reaction, with much less marked peri-bronchitis, or none at all. The involvement of the pleura in lungs infected solely with the influenza bacillus is very slight. There are hemorrhages into the pleura and perhaps a thin layer of fibrin upon the surface. The amount of fluid in the pleural cavities was always small, though blood-tinged. Empyema was found in cases secondarily infected with the streptococcus or pneumococcus. The involvement of the pleura may result from the extension of the inflammatory process along the interlobular septa and lymphatics, or, and this I believe is more commonly the case, from bronchiectatic cavities situated close to the pleural surface.

Gangrene of the lung was noted in one of the Camp Devens series in a case showing very extensive bronchiectases, with bronchiectatic abscesses. Extensive necrosis of the lung has

been observed in a number of cases in this same series and at the Brigham Hospital—necrosis due to organisms other than the influenza bacillus.

Organization in the pure *B. influenzae* cases was a common end result. The organization of the exudate begins early, certainly before the 10th day of the disease, and a prominent factor in bringing about this result is, I believe, the plugging of the bronchi with exudation. In patients who had survived three weeks or more there were very complicated gross appearances, due to extensive cicatrization of large portions of the lung. The contraction of interlobular septa, due to the avascular organization of exudate, causes marked distortion of the lobules of the lung, and peculiar lines of retraction on the pleural surfaces.

It is not the purpose of the present report to include the whole pathology of influenza. There are a few interesting features in other organs which are worthy of emphasis, however. Eight of the Camp Devens series showed waxy degeneration of the rectus muscles, and subsequent experience at the Brigham Hospital indicates that it was probably overlooked in some of the earlier postmortems done at Camp Devens. A number of these cases showed rupture and extensive hemorrhage into the rectus muscle. This lesion has been noted in other muscles; for instance, the transversalis, the internal and external oblique muscles, the latissimus dorsi, the pectoralis major and the intercostal muscles. The testes occasionally showed minute petechiae, but on the whole no striking gross change was observed. Microscopically very striking changes were encountered in nearly every case, namely, the cessation of activity in the seminiferous tubules; actual degenerative changes were frequently noted, and in late cases beginning fibrous tissue replacement of the degenerated tubules. This lesion of the testes seems to be wholly a toxic one, as there is very little cellular reaction. It is difficult to understand why such severe toxic lesions of the muscle and testes should occur. In the absence of effects attributable to toxins in other organs. For instance, the reaction of the spleen is very slight, the heart muscle rarely has shown any gross or microscopic lesion, and in general seems to escape entirely the toxic effect of the disease. Lesions of the adrenal, when extensive, such as hemorrhage, can be attributed to secondary infection, usually the hemolytic streptococcus. Minor acute lesions are constantly found in the cortex in influenza cases, but these lesions are similar to those found in many infectious diseases—the disappearance of lipid content, and focal necrosis with mononuclear phagocytic cell reaction. The head was opened in 20 of these cases. Infection of the middle ears was found in 13. Infection of the sphenoidal sinus in 20, frontal sinus in seven, and of the ethmoidal cells in eight cases. The bacteriology of the sinuses is given in the chart. Three cases showed punctate hemorrhages in the cerebral cortex.

BACTERIOLOGY

I do not intend to discuss at length the bacteriology of the epidemic. The table is a true account of the findings, and I prefer to have individuals draw their own conclusions. The opportunities for bacteriological work were particularly good.

CAMP DEVENS AUTOPSIES

No.	Duration	Type of lung	Remarks	Bacteriology	Sections
201	2 days.	Edema and congestion.	Purpuric rash.	Lung = No growth.	Skin—Streptococci in vessel thrombi. Lung—Streptococci in polys in bronchi.
183 * *	7 days.	Lobar (?) Bloody. Bilat. solidification.	Subcut. emphysema. No head.	Lung = Pure <i>B. influenza</i> .	<i>B. influenza</i> only in bronchi and alveoli.
203 *	7 days.	Bilat. lobar.	Waxy deg. rectus abd. Sph. } Sinusitis. Eth. }	L. L. = <i>B. influenza</i> + hem. strep. R. U. = <i>B. influenza</i> + hem. strep. R. L. = <i>B. influenza</i> + hem. strep. Sph. sinus = <i>B. influenza</i> + Pneumococcus IV.	Streptococcus.
207	8 days.	Lobar—left lower.	Fibrinous pleuritis. Fibrinous pericarditis. No head.	L. L. = Pneumococcus II. R. L. = Pneumococcus II.	Pneumococcus.
216	8 days.	Broncho-pneumonia, wet—bloody.	Waxy deg. rectus abd. Sph. Sinusitis.	L. U. } L. L. } No growth. R. U. } R. L. }	Large gram-positive cocci.
188	9 days.	Bilat. lobar.	No head.	Lung = Pneumococcus.	Pneumococcus.
197 *	9 days.	Bilat. broncho-pneumonia, confluent on right. Bronchiectasis.	Sph. Sinusitis.	L. L. = <i>B. influenza</i> + pneumococcus. R. M. = <i>B. influenza</i> + pneumococcus. R. L. = <i>B. influenza</i> + pneumococcus. Sph. sin. = <i>B. influenza</i> + pneumococcus.	<i>B. influenza</i> . Pneumococcus. Flat diplococci, Gram negative.
192 * *	10 days.	Bilat. confl. broncho-pneumonia. Bronchiectasis.	Emphysema of media. Emphysema, right 400 ccs. No head.	L. L. = <i>B. influenza</i> . R. U. = <i>B. influenza</i> . R. L. = <i>B. influenza</i> + pneumococcus.	L. L. } R. U. } <i>B. influenza</i> . L. U. } R. L. = <i>B. influenza</i> + pneumococcus.
195 * *	10 days.	Bilat. broncho-pneumonia. Confl. on left lower. Bronchiectasis.	Bilat. otitis media. Sph. } Sinusitis. Eth. }	L. L. = <i>B. influenza</i> . R. L. = <i>B. influenza</i> . Sph. sin. = <i>B. influenza</i> + pneumococcus IV.	<i>B. influenza</i> present. Predominating organism a Gram-negative diplococcus.
202 *	10 days.	Bilat. broncho-pneumonia.	Subcut. emphysema. Focal encephalitis. Otitis media. Sph. sinusitis. Waxy deg. Rectus abd.	L. U. = Staphylococcus aureus. L. L. = <i>B. influenza</i> . R. U. = As above. R. L. = As above. Sph. sin. = <i>B. influenza</i> + pneumococcus. Mid. ear <i>B. influenza</i> + pneumococcus.	<i>B. influenza</i> in bronchi. Gram-negative diplococcus found in superimposed exudate upon older broncho-pneumonia.
198 * *	12 days.	Bilat. broncho-pneumonia.	Emphysema of media. Otitis media. Fr. } Eth. } Sinusitis. Sph. } Waxy deg. rectus abd.	L. U. = <i>B. influenza</i> . L. L. = <i>B. influenza</i> . R. L. = <i>B. influenza</i> . Sph. sin. = <i>B. influenza</i> . Fr. sin. = <i>B. influenza</i> .	<i>B. influenza</i> predominates. Gram-negative diplococcus found in some sections.
193 * *	13 days.	Confl. bilat. broncho-pneumonia. Bronchiectasis.	Subcut. emphysema. Fr. } Sph. } Sinusitis. Eth. } Waxy deg. rectus abd.	L. U. } L. L. } No growth. R. U. } Sph. sin. = <i>B. influenza</i> + pneumococcus IV.	<i>B. influenza</i> in small numbers in two lobes. <i>B. influenza</i> & large cocci in two lobes.
204 * *	13 days.	Bilat. broncho-pneumonia. Bronchiectasis.	Subcut. emphysema. Otitis media-bilat. Sph. } Sinusitis. Eth. } Waxy deg. rectus abd.	L. U. } L. L. } No growth. R. U. } R. L. } Sph. sin. = { <i>B. influenza</i> . Hem. strep. Pneumococcus IV. <i>B. influenza</i> . L. mid. ear = { Hem. strep. Pneumococcus.	<i>B. influenza</i> in small numbers in bronchi.

CAMP DEVENS AUTOPSIES.—Continued

No.	Duration	Type of lung	Remarks	Bacteriology	Sections
214 *	13 days.	Lobar—rt. lower. Fibr. pur. bronchitis. Bronchiectasis.	Pneumococcus meningitis. Fr. } Sinusitis. Eth. } Bilat. otitis media.	L. L. = { <i>B. influenza</i> . Pneumococcus. R. L. = { <i>B. influenza</i> . Pneumococcus. Sph. sin = { <i>B. influenza</i> . Pneumococcus.	Rt. lower = Pneumococci. L. Lung = { <i>B. influenza</i> , great numbers in bronchi. Pneumococci in alveoli.
186 *	14 days.	Bilat. broncho-pneumonia. Bronchiectasis.	No head. Subcut. emphysema.	Cultures lost.	<i>B. influenza</i> . Streptococci. Large cocci.
215 * *	15 days.	Bilat. confl. broncho-pneumonia. Bronchiectasis.	Otitis media-bilat. Sph. sinusitis.	Lung = No growth. Sph. sin. = <i>B. influenza</i> . Fr. sin. = <i>B. influenza</i> + strep.	<i>B. influenza</i> in great numbers, pure.
211 * *	17 days.	Bilat. broncho-pneumonia. Bronchiectatic abscesses.	Otitis media-bilat. Sph. sinusitis.	L. U. = <i>B. influenza</i> + pneumococcus. L. L. = <i>B. influenza</i> . R. U. = <i>B. influenza</i> + pneumococcus. R. M. L. = <i>B. influenza</i> . R. L. = <i>B. influenza</i> + pneumococcus. Sph. sin. = lost.	<i>B. influenza</i> pure, great numbers except in bronchiectatic abscesses and according to lobes. <i>B. influenza</i> + pneumococcus in bronchiectatic abscesses.
212 *	20 days.	Bilat. broncho-pneumonia. Gangrene R. L.	Cerebral abscesses. Spleen abscesses. Otitis media-bilat. Fr. } Sinusitis. Sph. } Eth. }	Fr. sin. = <i>B. influenza</i> + pneumococcus II. R. M. E. = <i>B. influenza</i> + pneumococcus II.	Bacteria of all sorts.
219 * *	21 days.	Broncho-pneumonia—rt. Bronchiectasis.	Emphysema of media. Empyema-bilat. Veg. endocarditis-mitral. Otitis media-bilat. Sph. sinusitis.	No cultures. 9½ hours postmortem.	<i>B. influenza</i> in great numbers in alveoli and bronchial exudate. Mixed bacteria in bronchiectatic cavities.
223 * *	22 days.	Bilat. broncho-pneumonia. Bronchiectasis.	Fibrinous pleuritis. Chr. otitis media-bilat. Fr. } Sinusitis. Sph. } Eth. } Waxy deg. rectus abd.	No cultures. 12½ hours postmortem.	<i>B. influenza</i> in great numbers in alveoli and bronchial exudate. Occasional diplococcus.
226 *	22 days.	Bilat. broncho-pneumonia, advanced organization. Bronchiectasis.	Emphysema of media. Chr. otitis media-rt. Chr. sph. sinusitis.	No cultures. 13½ hours postmortem.	No bacteria except in granulating walls of bronchi, here pneumococcus.
218 * *	23 days.	Organizing broncho-pneumonia. Bronchiectasis.	Organizing pleuritis. Sph. Sinusitis.	R. U. = <i>B. influenza</i> . L. L. = <i>B. influenza</i> . R. L. = <i>B. influenza</i> , rare col. L. U. = No growth. Sph. sin. = <i>B. influenza</i> and pneumococcus.	<i>B. influenza</i> present. Pneumococcus predominates.
224 * *	26 days.	Organizing bilat. broncho-pneumonia.	Emphysema of media. Chr. otitis media-left. Sph. sinusitis. Waxy deg. rectus abd.	L. U. = <i>B. influenza</i> . L. L. = <i>B. influenza</i> . R. U. = <i>B. influenza</i> . R. L. = <i>B. influenza</i> + pneumococcus.	<i>B. influenza</i> (one slide).
227 * *	30 days.	Organizing bilat. broncho-pneumonia.	Fibrinous pleuritis-rt. Sph. } Sinusitis. Fr. } Otitis media-bilat.	L. L. = Contam. R. U. = <i>B. influenza</i> . R. M. = <i>B. influenza</i> + pneumococcus. R. L. = <i>B. influenza</i> + pneumococcus.	<i>B. influenza</i> in bronchi (four slides).
194 *	31 days.	Confl. bilat. broncho-pneumonia. Bronchiectasis.	Otitis media bilat. Sph. sinusitis.	L. L. = Hem. strep. R. L. = <i>B. influenza</i> + hem. strep. Sph. sin. = <i>B. influenza</i> + strep.	Streptococcus. <i>B. influenza</i> (one of seven slides).
213 * *	32 days.	Collapsed lungs, negative.	Empyema-bilat. Veg. endocarditis. Waxy deg. rectus abd. No head.	L. L. = <i>B. influenza</i> , pure. R. L. = <i>B. influenza</i> , pure. Pericard. = pneumococcus II.	<i>B. influenza</i> in bronchi and alveoli. Pneumococci in bronchi.
225 *	?	Lobar—L. upper. Gray hepatization.	No head.	No cultures. 12 hours post mortem.	<i>B. influenza</i> in bronchial exudate. Pneumococcus.
191	12 days.	Confl. bilat. broncho-pneumonia.	No head. Subcut. emphysema.	Lung = No growth.	



FIG. 1.

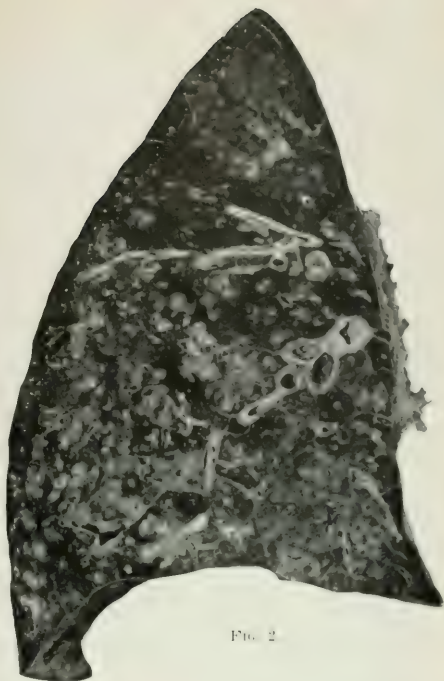


FIG. 2.

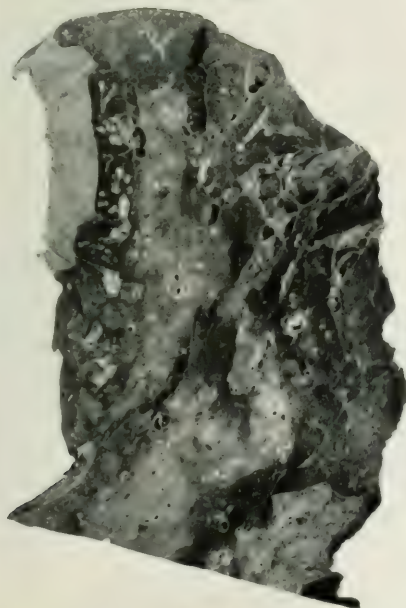


FIG. 3.

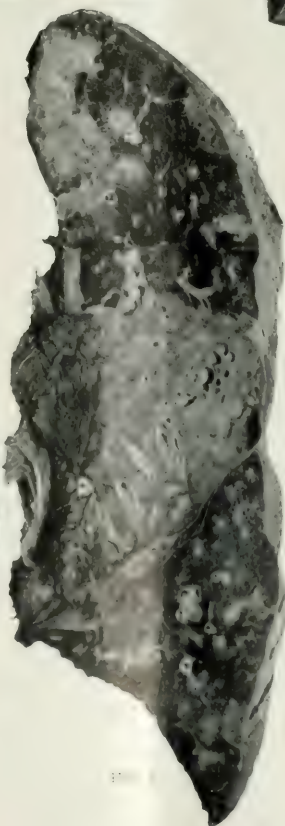


FIG. 4.

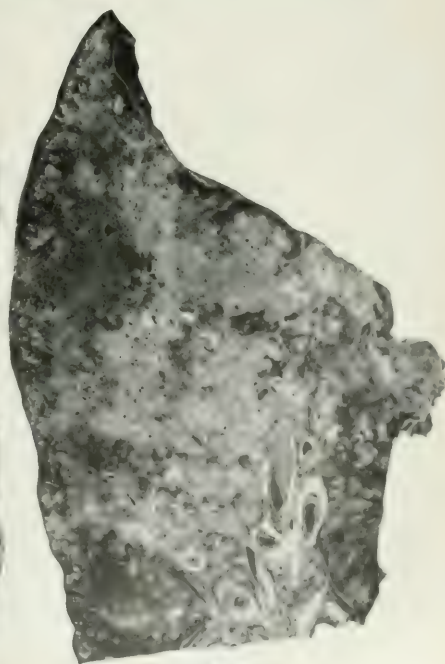


FIG. 5.

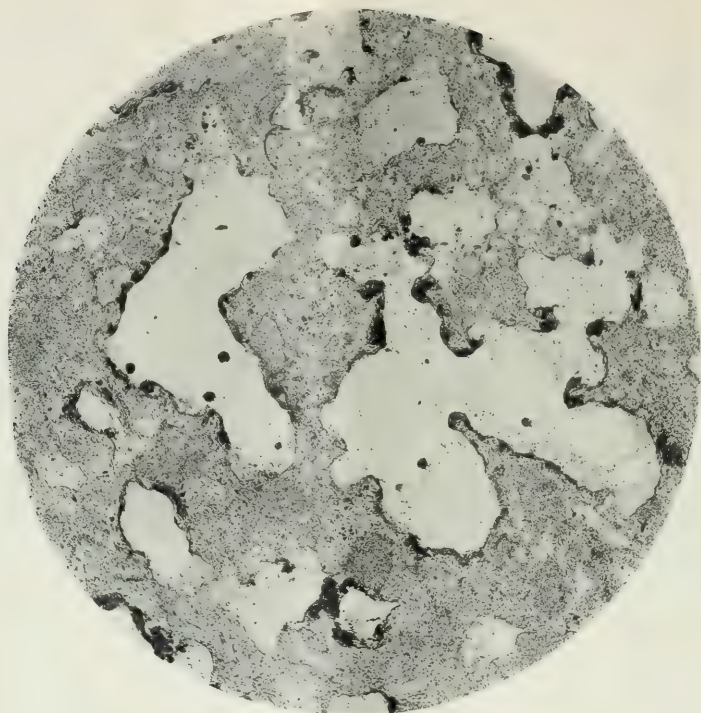


FIG. 5.

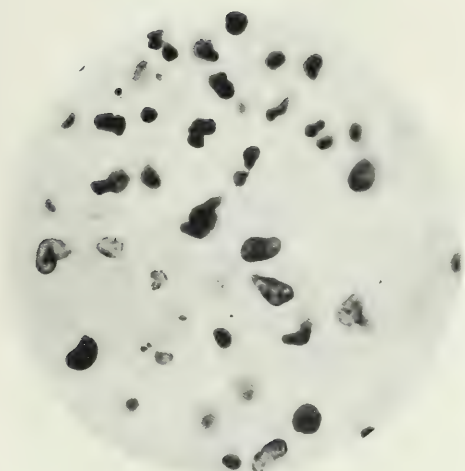


FIG. 7.

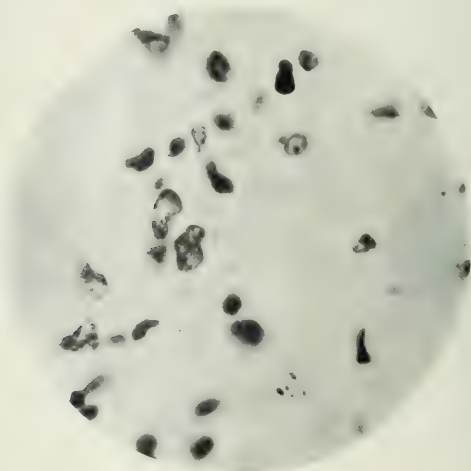


FIG. 8.

as the postmortems were done within a few hours after death, and the cultures were made and studied by myself. The bacteriological findings were further controlled by staining sections of the lungs for bacteria, the method employed being that of Giemsa. Because of their small size the influenza bacilli are easily recognized. It is interesting to note that in some early cases the bacilli were found not only in the bronchial exudate, but in the submucosa of bronchi and in the alveolar walls of the lung. Inspection of the chart will show that the influenza bacillus was found in pure culture in one or more lobes in nine of the 23 cases from which cultures were made. In sections of lungs from cases in which no cultures were made, influenza bacilli were found apparently pure in two cases, and mixed with other organisms in one case. In one case no influenza bacilli could be found. There were two cases of lobar pneumonia and one case with gangrene of the lung, in which no influenza bacilli were found. Of 28 cases by cultural and histological methods combined, *B. influenza* was demonstrated in 23 cases, and in 14 of these in pure culture. It is worthy of note that the bacilli were present in pure culture in a number of the late cases. In a number of cases in which influenza bacilli were not found in the lungs by culture, they were found in cultures from the sinuses of the skull or from the middle ear.

An analysis of the table of bacteriological results shows that the bacteriology of the lungs was mixed in a significant number of cases, but it also shows that the one organism occurring with greatest constancy, and in practically every case was the influenza bacillus. We may regard the pneumococcus, streptococcus, pneumobacillus, and the various micrococci encountered, as secondary invaders, without reasonable doubt. But are we justified in so regarding the influenza bacillus? It is extremely difficult to account for the epidemiological features of this pandemic if we accept the bacillus influenza as the cause. Our lack of knowledge of the pathogenicity of the influenza bacillus and our failure to reproduce the disease in man and animals with pure cultures is also a strong argument against its being the cause of

influenza. Yet, on the other hand, it is almost as difficult to explain the constant occurrence of the influenza bacillus in a series such as I have studied. One must keep in mind that our means of identifying the influenza bacillus are meager and that so far but few diagnostic criteria are available; and, by analogy, it seems almost certain that a group of organisms may exist having similar cultural and morphological properties, as is the case with the pneumococci.

The pathology of the lungs indicates clearly that we are dealing with a specific infection with a distinctive pathology in its early stages. The occurrence of *B. influenza* in pure cultures in the early stages is a fact of importance in the consideration of the etiology of influenza and I believe firmly establishes the existence of a *B. influenza pneumonia*.

EXPLANATION OF CHART AND FIGURES

CHART.—The following abbreviations are used:

L. U. = Left upper lobe.	Sph. = Sphenoid.
L. L. = Left lower lobe.	Eth. = Ethmoid.
R. U. = Right upper lobe.	Bilat. = Bilateral.
R. M. = Right middle lobe.	Confl. = Confluent.
R. L. = Right lower lobe.	

The stars in the first column indicate the presence of *B. influenza* in the lungs; double stars, in pure culture in one or more lobes.

FIG. 1.—Photograph of a Kaiserling specimen showing acute interstitial emphysema, characteristic of the early lesion in uncomplicated influenza pneumonia. Case 195.

FIG. 2.—Photograph of a Kaiserling specimen showing uncomplicated influenza pneumonia, of 17 days' duration. Case 211.

FIG. 3.—Photograph of a Kaiserling specimen of uncomplicated influenza pneumonia, of 26 days' duration. Note the extensive cicatrization with bronchiectasis. Case 224.

FIG. 4.—Interstitial emphysema in uncomplicated influenza pneumonia, of 13 days' duration. Case 204.

FIG. 5.—Low power photomicrograph, from an uncomplicated early influenza pneumonia, of 10 days' duration. Case 192.

FIG. 6.—Uncomplicated influenza pneumonia, of 17 days' duration, with extensive organization. Case 211.

FIG. 7.—Clump of influenza bacilli in alveolar exudate, early influenza pneumonia. Case 183.

FIG. 8.—Influenza bacilli in alveolar walls, early influenza pneumonia. Case 183.

PUBLICATIONS.

The following eight monographs:

Free Thrombi and Ball-Thrombi in the Heart. By J. H. HEWITT, M. D. 82 pages. Price, \$1.00.

Blood as a Lymphotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, \$1.00.

Primary Carcinoma of the Liver. By M. C. WINTERITZ, M. D. 32 pages. Price 15 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 191 pages. Price, \$2.00.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, \$2.00.

Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SEADEN, M. D., and MILTON C. WINTERITZ, M. D. Price, 15 cents.

Leukaemia of the Fowl: Spontaneous and Experimental. By HARRY C. SCHEISSER, M. D. Price, \$2.00.

The Structure of the Normal Fibers of Purkinje in the Adult Human Heart and Their Pathological Alteration in Syphilitic Myocarditis. By O. VAN DER STRICHT and T. WINGATE TODD. Price, \$2.00.

Other monographs will appear from time to time

PROCEEDINGS OF SOCIETIES

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

NOVEMBER 18, 1918

1. **Clinical Observations on Epidemic Influenza.** DR. A. L. BLOOMFIELD and DR. G. A. HARROP.

Published in the BULLETIN, January, 1919.

2. **Comments on the Pathology and Bacteriology of Fatal Influenza Cases, as observed at Camp Devens, Massachusetts.** DR. S. B. WOLBACH, Boston.

Published in the present issue, page 104.

DISCUSSION

DR. S. BURT WOLBACH.—There are a few points in the preceding paper by Dr. Bloomfield with which I wish to take issue. I believe that influenza is a disease of the respiratory tract; that in the respiratory tract we have the distinctive pathology of influenza. I believe that nearly every disease has somewhere in the body a lesion, and a fairly distinctive lesion, connected with it, and that the seat of infection in influenza is the respiratory tract. To explain the early involvement of the sinuses of the skull, for instance, we must regard them as part of the respiratory tract; at least the mucosa is in direct continuity with that of the respiratory tract.

In some localities, particularly the Naval Hospital in Chelsea, they have had a higher percentage of pure cultures of influenza bacillus than my series shows, and I think it is difficult to explain why the influenza bacillus happens to be the only invader of the lung in such a large proportion of cases. I dislike very much to go into reasons or evidence, in the lack of proof, but my own work has forced me to the conclusion that influenza is a disease of the respiratory tract, and that this is the one part of the body where the lesion constantly occurs; but I shall not advance arguments one way or the other in regard to the etiology of influenza. As a matter of fact, I do not believe that any argument regarding the habits of the influenza bacillus in culture tubes or in tissue, or in association with other bacteria, is worth a great deal, but I think the reasons are many for believing that we may have to deal with a particularly virulent strain of influenza bacillus. We are all familiar with the variation in behavior of strains of streptococcus, such as occur in milk-borne epidemics, where the streptococcus achieves extreme virulence. The fact that there has been in the neighborhood of Boston during the past few years a number of small epidemics of streptococcus infection may explain the large number of influenza cases complicated with the hemolytic streptococcus that we have had at the Brigham Hospital. I have already said that we know very little about the influenza bacillus, and I feel that I have presumed a great deal in identifying certain organisms as influenza bacilli, but according to our present knowledge they must be classified as such. They all have a certain morphology, they all are Gram-negative, they require hemoglobin for cultivation, they will not grow in ordinary media or at room temperature,

and though I place some value on their behavior in association with other bacteria, I feel that all of our criteria taken together are indeed very slight for the identification of the influenza bacillus.

I feel somewhat secure in the position I have more or less arbitrarily taken this evening for purposes of discussion, and for which I think I have considerable evidence, though the evidence is not proof. I should feel much stronger in my position that the influenza bacillus is the cause of influenza were it not for the fact that I have had small chance to investigate the early type of extensive lung involvement with positive bacterial findings. This is a weak point in such evidence as I have.

DR. W. W. FORD.—I would like to say a word or two about some of the points referred to which have been interesting us in the bacteriological laboratory of the School of Hygiene. One of the first statements to be made in regard to the influenza bacillus was that this epidemic was occasioned apparently by an organism which was different from the influenza bacillus which has been isolated from time to time from various cases during the past 10 years—an organism which differed somewhat from the clear-cut influenza bacillus which we have come to regard as typical.

It is interesting to note that in the large series of cultures of the influenza bacillus my associate, Mr. Robinson, has been receiving from Washington, organisms isolated from the present epidemic, one can make out about as many variations in morphology as those shown by the organisms isolated before the epidemic. At first, the cultures seemed to be clearly and unmistakably different, and yet from good photographs and drawings it is evident that the variations of morphology are quite as great and quite as distinct as the variations which have been described previously from time to time.

I think it is interesting at this time to call attention to a remarkable similarity between our ideas concerning influenza and our ideas concerning the only animal disease which can be compared with it. I refer to hog cholera. In 1888, Dr. Smith isolated the bacillus from a typical epidemic of the disease, reproduced the disease, and everyone became convinced that the organism was the cause of it. Subsequently, Dr. Welch was able to reproduce the ulcers in the mouth regarded as diagnostic. Gradually, however, some doubt was thrown on this belief. The first definite statement in contradiction was a publication by De Schweinitz, who said that he had been able to reproduce the disease with the serum with all its clinical manifestations, but with no trace of the bacillus. Since that time there have been many epidemics of hog cholera where the bacillus could not be found and yet the disease could be reproduced with a virus. The reactions are very clear and distinct. At the same time in the natural disease there are many cases of hog cholera in which we do find the bacillus. We have the same thing in influenza. If we hypothesize that there is some other cause for this disease I think the analogy would be almost complete.

Just a word or two calling attention to the public health aspect of influenza. Dr. Howard's point in regard to restrictive measures should be emphasized, for there is no evidence that any of the restrictive measures which were undertaken had any influence in checking the spread of this disease. It is a question whether it is wise to carry out the drastic restrictive measures which were attempted. When one comes, however, to a consideration of a pandemic such as occurred here, then health authorities are certainly justified in carrying out any measures that can be suggested, not because there is evidence that the disease may be thus controlled, but on account of the economic question. From an economic standpoint we are justified in applying restrictive measures, but I fail to see that any such measures have in any way influenced the spread of the disease or have altered it in any particular.

DR. W. G. MACCALLUM.—When Dr. Welch returned from Camp Devens he reproached us with bad technique because we did not find the influenza bacillus in all our cases. It is a relief to see Dr. Wolbach's specimens, because they correspond closely in form with those in which we did find the influenza bacillus, but are quite different from those studied at Camp Lee and in this hospital in which we did not find the bacillus.

It seems possible that there are local differences in the bacterial flora in different states, so that Massachusetts may be infected with the influenza bacillus while it is not so in Virginia and other places. Late reports from Chicago and other cities describe the pneumonia as due to the pneumococcus.

In view of the fact that we have always found the influenza bacillus as an occasional invader and now find that it can produce alone a peculiar type of pneumonia, I still believe that there is some other cause of the epidemic disease influenza and that the influenza bacillus, like the streptococcus, staphylococcus and various types of pneumococcus, is merely a secondary invader.

I have been much impressed with the resemblance of influenza to such a disease as measles, because in the previous epidemic measles so affected the respiratory tract as to allow the invasion of various bacteria, including even the influenza bacillus. Now we have the influenza lowering general resistance and perhaps sensitizing the respiratory tract to invasion by any organism which happens to inhabit the throat.

DR. S. E. HOWARD.—I think Dr. Bloomfield gave the main points of my findings. The influenza bacillus was never found in the blood. In the sputum it was the predominating organism in about 8 per cent of the cases; it was also found in about 30 per cent of the sputum cultures, but not as the predominating organism. In cultures from the nasopharynx it was frequently present, but only in one case was it the predominating organism in a patient who had influenza. A few control cultures were taken from people who did not have influenza and in one of these the influenza bacillus predominated.

DR. WM. T. HOWARD.—I have been greatly interested in these papers. At the beginning of the epidemic I read all the literature I could on the subject, and I could not see that we

had any ground to hope that by restrictive measures we could interfere with the number of cases which would occur in a crowded city. I could see how, perhaps, the number in a community at any one time might be modified, but not that the total number of cases would be influenced at all. Therefore I was opposed to any unusual attempts at restriction, and I would be very glad if Dr. Bloomfield would tell us if the evidence he has points in this direction.

I would like to ask several questions. Can we clinically make a diagnosis with any certainty between lobar pneumonia and bronchopneumonia in the great mass of cases in these influenza epidemics? From the standpoint of statistics this is a matter of great importance. It seems to me very unlikely that such a differential diagnosis can be made correctly in many of these cases. This has been attempted in Baltimore. There the doctors have had more fatal influenza cases with lobar pneumonia than cases with bronchopneumonia as the contributory cause of death.

Another question is, What is the explanation of the large number of cases of pneumonia independent of influenza during these influenza epidemics—that is, primary pneumonia, apparently not occurring as a complication of influenza? This has occurred in all the severe epidemics that have been accurately studied, and it is well known that the year after such epidemics we get a large increase in deaths from acute diseases of the respiratory tract.

Perhaps it would interest you to know something of the disease as we saw it from the health department. It started here about September 20, apparently on the east side of the city. The first cases we heard of occurred in the private practice of two physicians who were also health officers. The early cases were almost entirely among men working at the government construction camps. These physicians told me at first that the disease was entirely a disease of men; but in a few days they changed their tune. The men who had the disease were mostly married, and in a few days their wives came down with it and shortly afterwards their children, and in many families all the children. The disease spread rapidly at Locust Point, where many men work on ships as stevedores, or on repair work of steamers from Europe. We lost over 3500 people in Baltimore in the month of October by death in connection with this epidemic. There were a great many deaths in which pneumonia was given as the sole cause, and I am anxious to find out whether there have been cases of pneumonia in which the influenza attack has been so mild that it has been overlooked. The death rate from a number of other diseases was also very materially affected. The number of deaths from pulmonary tuberculosis was enormously increased, over 50 per cent; from Bright's disease 25 per cent. There was a remarkable increase in deaths from diarrhea and enteritis in children under two years of age—something over 100 per cent. Deaths from heart disease increased almost 100 per cent. Diphtheria went up markedly, entirely out of proportion to the number of cases usually present. The number of deaths from whooping-cough increased four or five times.

All this, of course, from the standpoint of the public health administrator is very interesting. Here is a calamity—you cannot possibly control it, and it leaves us with a number of unanswered questions.

DR. L. V. HAMMAN.—The epidemic we have passed through is now nearly over; only a few cases remain in the hospital. However, judging from what has occurred in other epidemics, we are not yet to congratulate ourself upon the epidemic being over, for fresh outbreaks, more limited it is true, may be expected during the winter. At least we have come upon a breathing space and may pause to look back over our experiences and see what fresh information we have gained about the disease.

Following the great epidemic of 1847-49, masterful clinical pictures of influenza were drawn emphasizing all the important clinical and epidemiological features of the infection. It is an inspiration to turn back to these unexpectedly clear, concise, and accurate descriptions.

Following the next great epidemic in 1889-90, an advance was made furnishing still more precise and detailed descriptions of the clinical symptoms, elaborate pathological studies, particularly of the pulmonary complications and bacteriological investigations. During the period from 1850-90, pathology and bacteriology had become highly developed disciplines, and physicians were prepared to study infectious diseases with exact methods which were unknown at the time of the previous epidemic, when acute clinical observation was the only important method of observation. The result of these studies has given us clear and accurate descriptions of the pathological anatomy and of the bacteriology of the pulmonary complications. Either pneumococci or streptococci were found to be the almost constant cause of the associated bronchopneumonia.

Two years after the epidemic was over, Pfeiffer published his discovery of the influenza bacillus. Dr. Bloomfield has stated that his published data do not carry the conviction that the influenza bacillus is the cause of influenza. I quite agree with him that they do not, but Pfeiffer's claims have been accepted, since no opportunity has come since then to test them out.

After the present epidemic is over, I feel sure that the clinical picture of the disease will be filled in with still greater detail. Perhaps our notions of its place amongst the infectious diseases may change. It certainly has many of the features of the exanthemata and while these features have been pointed out before, their importance has not been emphasized. Also, our knowledge of the pathology of the pulmonary complications will be enriched. However, the one great opportunity of the present epidemic is to settle definitely the relation of the Pfeiffer bacillus to the disease. Returns of investigations are rapidly coming in from all parts of the country. Unfortunately, they are not all in accord: indeed, the greatest discord exists. For the present, I must take my stand entirely upon the work done in this clinic, but on the basis of this work I unhesitatingly proclaim my conviction that the Pfeiffer bacillus is not the specific cause of influenza.

DR. S. B. WOLBACH.—I am perfectly willing to concede a great deal on this question of etiology. Everyone has been kind enough not to mention this evening the fact that Nicolle has already announced the discovery of a filterable virus for influenza. There was an account of it in the last number of the *Journal of the American Medical Association*. Nicolle was able to produce grip-like sensations in man and monkey, with an incubation period of six days, by the injection of filtrates of secretions diluted with salt solution from influenza cases. Before this announcement appeared, Dr. Rosenau and his associates at the Naval Hospital in Chelsea, made similar attempts without success. They excluded the possibility of a filterable virus. A filterable virus, as you know, has already been reported for common colds. This organism has been cultivated and resembles the globoid bodies of poliomyelitis. I refer now to the work of Foster. The experimental evidence for this organism being the cause of one type of common colds is very good, as Foster reproduced the disease in volunteers with his cultures. It seems possible that Nicolle may have encountered the same virus that Foster found. When I went to Camp Devens one of the first things about the epidemic emphasized by Major Churchill, who was then chief of the medical service, and a prominent pediatrician of Chicago, was the striking similarity of the initial stage of influenza to measles, but here again measles may very well be, I believe is, a disease of the respiratory tract.

JANUARY 29, 1919

1. A Functional Re-education Clinic: Organization and Methods. DR. W. G. THOMPSON, New York.

My talk this evening really is not a talk, but an exhibition of lantern slides. Referring to the work in which recently I have been interested in New York, and the clinic which I have organized, the story is briefly this:

A long-time friend, a patient of mine, came to me about a year and a half ago and asked if I would not take over and equip a base hospital, to be placed under the charge of the French Government for its use. For this purpose she put a large sum at my disposal. I was to secure the staff and equip the hospital in this country and act as its agent here. But the difficulty of securing the personnel, because so many of our men had already gone abroad, or wanted to wait and go under the United States Government, caused this project to be abandoned.

I had been reading about the wonderful work being done in England and France since the onset of the war, in the reconstruction and re-education of the mutilated. I was convinced that there was a wide field in this country for such work, and, so far as I could see, there was no institution organized here for that purpose; hence, there seemed to be a fine opportunity to organize an institution for functional re-education.

We talked the matter over and were convinced that such an institution was needed for the re-education of the industrial worker after the immediate wants of the returning soldier and

sailor had been met, and that the institution ought to be continued for the men who had been so unfortunate as to have been maimed or mutilated, possibly on the railway, in the factory, or in a street accident, if you will, but for which at the present time there is very inadequate after-treatment provided.

Take, for instance, a large hospital like Bellevue. A man is brought there badly injured. An amputation is performed, and when the wound is healed the man goes out, recorded as "cured." It is true that the social service workers interest themselves in seeing that such a man is provided with an artificial arm or leg, as the case may be, but training him to use his muscles and nerves to the best advantage is not provided, and this is the work we are doing.

I think you will be surprised at the extent of the literature already published on this subject. Bibliography of 40 pages [passed around], gotten up by The Red Cross Institute for Crippled Soldiers, has been compiled from articles written and published in England, France, and Italy, and before we got into the war, in Germany. This is a very considerable literature to have been developed in this short time. It gives one a little idea of the work that has been done and is now being done on the other side.

[Lantern slides were here shown of reconstruction hospitals in France and England, and Dr. Thompson's Clinic, as well as pictures of the individual workers in these institutions, showing the varied utilization of the new apparatus for armless and legless men. This contrasted with a picture of Captain Cuttle with his iron hook and Peter Stuyvesant with his wooden peg for a leg, to emphasize the strides in modern help for the maimed and mutilated. Pictures were shown of the apparatus for mechanotherapy devised by Major R. Tait McKenzie, M. D., of Philadelphia, now in use in the Clinic for Functional Re-Education, organized by Dr. Thompson, in New York, with some of the apparatus devised by Prof. E. A. Bott, of Toronto, and Major R. Tait McKenzie, of Philadelphia, full explanation of the methods of work being given by Dr. Thompson. Pictures also were shown with descriptions of this clinic and hospital with its complete equipment for hydrotherapy, mechanotherapy, electrotherapy, etc.]

DISCUSSION

DR. WELCH. Is a survey being made among the employers as to the possibility of these men being put into any trade?

DR. THOMPSON.—We are not doing that work. Our work is on the side of functional treatment, and we are trying to keep within that line, but the Red Cross, in the spring of last year, had a fund of \$50,000 given for the purpose of establishing an institution which would look after the vocational training and make such a survey. A very extensive survey was also made in Pennsylvania. Too many trades are undesirable, and if you concentrate on teaching eight or ten trades, it is possible that many of the men can shortly be trained to make their own living.

MRS. HENRY M. THOMAS. Is this the local branch of the Red Cross?

DR. THOMPSON.—It is part of the national organization to which I refer, under Mr. Douglass C. McMurtrie.

I might say in regard to the organization, that we have, of course, an orthopedic surgeon at the head, and an assistant surgeon, who is on duty all the time to examine new cases, and see that the histories are carefully recorded, etc.

Stenographers record all histories. Instead of trained nurses exclusively having the care of the patients, we have 35 volunteer aids. The social service work is also a most interesting one. In asking the men what work they prefer to do, it has been found that the marines, while undergoing functional treatment, usually select typewriting and Spanish. Because of this, we sent out and got 12 typewriting machines and are giving them typewriting lessons. Our X-ray man speaks Spanish and he is giving instruction in Spanish. The men feel that the great opportunity for trade in the future for this country will be with South America, and they feel that knowledge of Spanish will be most useful in what they look to be a great field. We, of course, also have a number of entertainments for the men.

DR. WELCH.—I think this is one of the great outcomes of the war that one likes to think of—the compensations that are discovered in the great development work of so-called re-education and vocational training. Not that it was altogether unknown before, but it has received a tremendous impetus and the public has come to have some sort of an understanding of what is being done. I recall when it was first talked of that Dr. Winford Smith said: "That is exactly what the properly organized ordinary civic hospital should feel its function to do. For the surgeon to send out a maimed and mutilated man is not satisfactory—that man first should be re-educated and taught." This is a broadening of the idea of what should be the function of a hospital to a community, of course, is one of the results of this work.

Dr. Thompson has identified his name with this line of work and he has done a splendid service.

I was not fortunate enough to hear Sir Arthur Pearson when he was here the other night and spoke to our medical society, although no doubt many of you here to-night did have that pleasure, but I did hear him at an after-dinner talk in Washington and he was tremendously thrilling and stimulating. He brought out one point particularly—that the gain is re-education, which is also bringing a broadening of personality of the individual. These blinded, re-educated persons are cleverer and have more brains than ever before. As the Secretary of War expressed it: "They are removed from the tyranny of one faculty. We do not know it, but we are under the tyranny of one faculty, our eyesight. A man who has previously been engaged in some other occupation requiring some kind of intellect, is so much the keener, so much cleverer than he was before, that his ordinary capacity is much greater than before." He gave one or more instances. It was a most inspiring and thrilling talk of the outcome of the war, and was a great contribution to what the duties and obligations of the country are to our disabled soldiers and sailors and also to the

industrial workers. It is an obligation of the government to restore the men it has called from civil life, to do its great work for civilization, to other occupations in which their lives will be in as nearly good condition as when it took them. This is a plain obligation. I do not know, and we cannot tell except from experience, how successful we are going to be. I confess I am somewhat apprehensive about whether we are going to be as successful in this line of work as they have been in England and France. I am frank to say that I do not think this responsibility should be divided among the three agencies—an entirely new outside civilian agency, such as Dr. Thompson referred to, the War Risk and Insurance Division and the Division of Physical Reconstruction of the United States. With these provisions, unless a man follows the lines they are obliged to follow, I do not see that it is any protection, or at least it is a very limited protection. The fact that there is no centralization, that a man passes from one agency to another, from the medical to the civilian, makes it for the moment a very unsatisfactory instrument. It is improving very much under our surgeon-general, who is a very able man, and I think it is getting better all the time.

We are very much indebted to Dr. Thompson. I am certain that we have a great deal to learn here at Johns Hopkins Hospital. I am sure we are not beginning to do our duty in this line, but at least we are awakening to what is our duty—to see that a patient is not sent out handicapped and disabled as a result of wounds.

DR. MILTON J. ROSENAU, Professor of Preventive Medicine and Hygiene, Harvard Medical School.—Dr. Welch has asked me to tell what we are doing at Harvard in industrial hygiene. I do not know what excuse there should be for me to speak on the movement of industrial hygiene at Harvard, unless it rubs elbows closely with the subject that has just been presented so illuminatingly by Dr. Gilman Thompson. Industrial hygiene is a very important chapter in preventive medicine, and I have regretted very much for years that we have had so little active work along this line in our country. Through the inspiration and zeal of Dr. Frederick C. Shattuck, Emeritus Professor of Medicine, Harvard Medical School, quite a large sum of money—it seems large to us—was gathered for a number of years for the purpose of research and teaching in “industrial health.” The enterprise thus hatched was put in charge of a Committee on Industrial Hygiene, including Dr. F. C. Shattuck, Dr. D. L. Edsall, Dr. Reid Hunt, Dr. M. J. Rosenau, and Dr. C. K. Drinker. I think the only reason I was made a member of the committee was to be sure that the new movement of industrial hygiene would co-operate with our school of public health. It was plain to our committee that no one department could cover such a wide field as industrial hygiene. Industrial hygiene at Harvard, therefore, is not a department; it is not a division; it is not a separate school; it is just industrial hygiene, but doubtless it will soon find a nest.

Now, we proceeded on three lines: one, research; two, teaching; three, publication. I will take a few minutes to outline a few important points about each one of these three.

(1) *Research*.—We have decided to concentrate as far as possible on a few lines, rather than scatter our efforts. One of the problems of industry at present being studied is manganese poisoning, an industrial poisoning about which comparatively little is known and towards which a certain amount of progress has already been attained. Another problem soon to be studied is the sanitation of mercantile establishments. By “mercantile establishments” we mean the large department stores, and until you look into this question with more or less thoroughness one has no conception of the inadequate handling of the problem. A special fund has been provided for this study, which interlocks with sociology, economics, sanitation, and preventive medicine. These examples are cited to give you an idea of the kind of research we are trying to do.

We have made a resolution not to butter our bread too thin. In other words, it is the intention of the committee on Industrial Hygiene to concentrate in certain directions, and we have selected first to develop industrial physiology; industrial chemistry will probably come next.

(2) *Teaching*.—This is on three different levels. Our chief object is to train physicians to take charge of the personnel in large industrial establishments. Those in charge of these stations now have learned their job through experience, and some have made good, although this work is mostly done in an unsatisfactory way. Courses are given in industrial physiology, industrial pathology, toxicology, preventive medicine, and the legal side of industrial medicine. Use is made of the industrial clinic under the charge of Dr. D. L. Edsall, at the Massachusetts General Hospital. The curriculum provides for intensive training, which runs about four months in the theoretical sciences, which are fundamental. Following this, we provide practical work in what we call our industrial clinics. In other words, arrangements have been made with industrial physicians in several large establishments in and around Boston to take our students. The students go to these establishments not simply as on-lookers, but are required actually to assist in the work for a certain period of time under the direct supervision of the physician in charge. In this way, our students spend some weeks with Dr. F. E. Schubmehl, of the General Electric Company; Dr. W. Irving Clark, Jr., of the Norton Grinding Works; and Dr. W. F. Dolan, of the Fall River Ship Yards. We have also made arrangements with other establishments, so that all our students may get the industrial point of view and learn the problems of industry before taking charge of establishments on their own responsibility.

For those who desire to carry out original research, ample opportunity is afforded in the various departments of the Harvard Medical School, and such work may be offered for either the degree of Doctor of Philosophy or the degree of Doctor of Public Health.

On the third level are those who want to be inspectors or industrial aides. I am inclined to develop this a little in detail for the reason that it is in line with Dr. Gilman Thompson's work in the New York Clinic for Functional Re-Education of Soldiers, Sailors, and Civilians. It seems that most of

the men and women who are at present doing physiotherapy have obtained this training from dancing masters or institutions for physical training of the type of Mulholland's. In this work, we co-operate with Dr. Lovett and the children's hospital work. A school has been started to train women to do the things which the volunteer workers are now doing along the lines of physio-therapy and reconstruction. For the present, this work is fostered by the War Department for its injured soldiers, but we are fully alive to the fact that reconstruction for the military establishment is a comparatively small problem and will not last very long; that is, it is small and temporary as compared with the reconstruction work required for the industrial work. The number mutilated in railroads, mines, and industry have not been given the attention that the subject warrants, and which has been so clearly set forth by Dr. Gilman Thompson this evening.

(3) *Publication*.—I am happy to be able to report that we have started a *Journal of Industrial Hygiene*. The first issue will appear in May, and will come out every month. It will contain original articles, reviews, and literature on the subject, covering a wide field. The *Journal of Industrial Hygiene* will be edited by Dr. D. L. Edsall, with a staff of associate editors, including Dr. W. I. Clark, Jr., Dr. Alice Hamilton, Dr. Y. Henderson, Dr. H. E. Mock, Dr. J. W. Schereschewsky, Dr. C.-E. A. Winslow, and Dr. W. H. Howell; and managing editors, Dr. K. R. Drinker and Dr. C. K. Drinker.

We naturally expect that a journal of industrial hygiene will help stimulate work in industrial hygiene, not only in this country, but abroad, for it will be international. I think you will agree with me that it will doubtless serve a useful purpose.

DISCUSSION

DR. THOMPSON.—How are you going to arrange your courses as to those who already have positions as industrial physicians and those who want to be trained for this work?

DR. ROSENAU.—In addition to the regular courses, we have provided for special students. To those who take full course we offer either a certificate or a degree; special students who are qualified may take particular work to fit them better for their responsibilities.

DR. THOMPSON.—Then it is like a post-graduate course?

DR. ROSENAU.—In part.

Malaria in the Federated Malay States. A Correction. DR. W. G. MACCALLUM.

In the March, 1918, number of this BULLETIN, in discussing Col. Whitmore's paper, I evidently made a misstatement with regard to the death-rate for malaria in the Federated Malay States. My attention has been called to this by the Executive Engineer of Public Works in Kuala Lumpur and by Dr. Stanton in letters and I am anxious to correct it. I spoke from memory of a conversation with Mr. Evans, the engineer, who showed me the system of drains constructed for the purpose of combating malaria, and intended to convey the impression which I had received, that among the coolies actually engaged in these excavations, that is, in the most dangerous exposure, the mortality reached those extraordinary figures. But that even in this particular case this estimate was wrong appears from Mr. Evans' letter, in which he states that "the worst individual estates I can call to mind have not exceeded a general death-rate of 600 per mille in any one year." His report for the year 1916 gives the following figures which bear upon the actual general and malarial death-rates:

Year	Population	No. of deaths	Death-rate
1911	1,045,947	40,914	39.11
1912	1,081,799	40,961	37.8
1913	1,117,625	38,000	34.0
1914	1,136,500	39,000	34.31
1915	1,172,336	33,899	28.92
1916	1,208,177	36,981	30.6

Malaria fever accounted for 17,627 deaths or 47.66 per cent of the total deaths. The death-rate per thousand of the population from malarial fever was 14.58 as compared with 12.97 in the previous year.

The total deaths and mortality rate from malarial fever for the past six years are set out below:

Year	Deaths	Per cent	Per mille
1911	17,440	45.02	17.47
1912	17,870	44.02	16.52
1913	16,414	43.19	14.69
1914	13,634	34.95	11.99
1915	15,208	44.0	12.97
1916	17,627	47.66	14.58

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THE EFFECT OF DIET ON THE HEALING OF WOUNDS*

By ADMONT H. CLARK, M.D.

(From the Pathological Laboratory of The Johns Hopkins University, Baltimore)

The work of Hooper and Whipple¹ on blood regeneration after anemia shows that specific diets produce a very marked effect. The rate of blood regeneration on a meat diet is very rapid, a matter of days or a few weeks; whereas, on a diet rich in carbohydrate it is very slow, months being sometimes required for complete regeneration. These results suggested the possibility that specific diets might influence the rate of wound healing and the following experiments were accordingly undertaken.

Carrel^{2,3} has studied the process of wound healing in both men and animals and has found that the curve representing the diminution in size of an aseptic wound while it is cicatrizing is regular and geometric. From Carrel's curves Du Noüy⁴ has derived mathematical formulae, by means of which the area of a wound at any given date can be predicted. His formulae are:

$$S - S' = i \sqrt{T - t} \quad (1)$$

$$S'' = S' [1 - i(T' - T - t')]. \quad (2)$$

S represents the original area of the wound.

S' = area t days later.

T = time from first observation and = t in (1).

t' = time from S' to S'' .

i = constant coefficient which is characteristic of the wound and which varies with the size of the wound and the age of the patient.

After calculating i from (1) S'' can be predicted with a remarkable degree of accuracy, any deviation from the calculated curve showing the presence of an infection.

In his experimental work on animals^{2,3} (dogs, guinea-pigs and cats), where the wounds were kept as sterile as possible, Carrel found the process of cicatrization to be divided into four parts:

(1) *Quiescent Period*.—During this period there is no contraction and the main characteristic of the period is its variable length, 1-5 days.

(2) *Period of Gradual Contraction*.—During this period the wound contracts at a rate which is proportional to the size of the wound.

(3) *Period of Epithelialization*.—The epithelium begins to form and the process of healing may now continue by epithelialization alone or by epithelialization and contraction together.

(4) *Contracted Period*.—After the wound is healed the wound enlarges.

* The experiments reported in this paper were carried out by Dr. Clark during the spring of 1918. Owing to Dr. Clark's death the results which they show are of a preliminary nature and represent incomplete work. I thought them, however, of sufficient interest to publish, hoping that they might suggest further work along the same line.—JAMES HOWELL CLARK.

No previous work on the effect of specific diets on wound healing has been reported.

EXPERIMENTAL METHOD

Twelve dogs as nearly the same age, size and general condition as possible were chosen and three were put on each of the following diets:

(1) *Mixed Diet*.—41 gm. of fat (lard or butter) and 107 gm. of lean meat (beef or liver) were boiled together, then mixed with 354 gm. of bread and run through a meat chopper. This was divided among three dogs.

(2) *Carbohydrate Diet*.—500 gm. of bread moistened with water were divided among three dogs.

(3) *Protein Diet*.—500 gm. of lean meat, either round of beef or liver, were boiled and divided among three dogs.

(4) *Fat Diet*.—300 gm. of fat (equal parts of butter and lard) were boiled and ground with 100 gm. of bread.

The dogs were fed on these diets for three days before the wounds were made. Throughout the experiments the dogs were weighed and the weight was found to remain practically constant.

Preliminary experiments with various types of dressings showed that the wounds healed better and showed less tendency to infection when left entirely open with no dressing of any kind. The dogs were given ether anaesthesia, the backs were shaved and two circular skin flaps (one large and one small) were removed from each side of the back. The wounds were placed where the dog could not lick them and were left open. As soon as they were made, the size of the wounds was traced on a piece of transparent celluloid with a wax pencil and similar tracings were made at intervals of three or four days throughout the experiment. These areas were copied on heavy tracing paper and measured in square centimeters by means of an Amsler polar planimeter. If a wound showed marked infection the results were discarded.

A second set of wounds was made after the first had healed and finally a third set in which the dogs were interchanged in diets.

RESULTS

I. Effect of Diet on Wound Healing.—The results for Sets I and II are averaged in Fig. 1. The large and small wounds are averaged together; the area given being the total wound area on one dog (*i. e.*, the area of two large and two small wounds). As there were three dogs on each diet in each set, each curve shows the average result on six dogs. The diet seems to affect the length of the quiescent period. The protein-fed dogs have no quiescent period, the contraction beginning at once. The carbohydrate dogs have a quiescent period of three days, those on the mixed diet, of four days, and the fat-fed dogs, of six days. After the sixth day the curves run parallel and the dates of final healing differ by the same amount as the lengths of the respective quiescent periods.

The diet, therefore, is a factor in determining the date of the beginning of Period II, the period of granulous contraction.

In Set III, four dogs which had been on a fat diet in Sets I and II were put on a protein diet. The results shown in Fig. 2

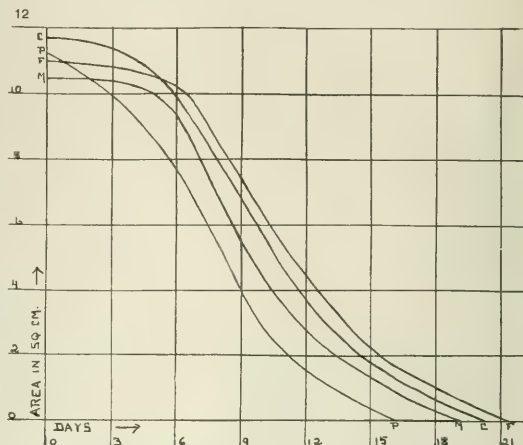


FIG. 1.—Effect of Diet on Wound Healing.

Average results of Sets I and II.

C = carbohydrate diet.

P = protein diet.

M = mixed diet.

F = fat diet.

Abscissæ = time in days; ordinates = wound area in sq. cm.

give the same result as Curve I, though not so markedly as might be wished. I believe that there should have been an

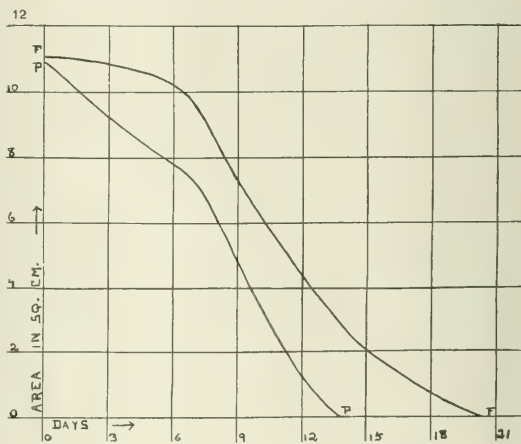


FIG. 2.—Effect of Change in Diet.

Curve F gives results for fat-fed dogs in Sets I and II.

Curve P gives results for same dogs fed on protein diet in Set III.

Abscissæ = time in days; ordinates = wound area in sq. cm.

interval between the two sets of experiments during which the dogs could be fed on the new diet. In this experiment Set III

was begun as soon as Set II was finished and the change in diet was simultaneous with the making of new wounds.

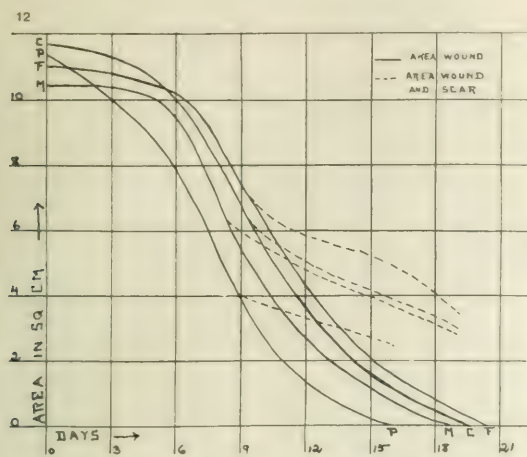


FIG. 3.—Curve Showing Formation of Epithelium.

--- area of wound and scar.

— area of wound.

Abscissæ = time in days; ordinates = wound area in sq. cm.

In Fig. 3, the progress of Period III, the period of epidermization, is shown, the dotted line indicating the area of the wound and the scar, the heavy line the wound area.

It is evident that the formation of the epithelium starts on the same day, irrespective of the diet and the size of the wound.

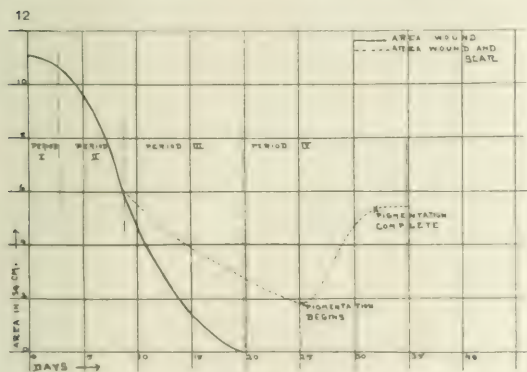


FIG. 4.—Average Curve for Sets I and II (all Diets).

--- area of wound and scar.

— area of wound.

Abscissæ = time in days; ordinates = wound area in sq. cm.

Contraction continues throughout Period III and the closing of the wound is due to a combination of the two factors, contraction and epidermization. The dotted curves giving the area of wound and scar are parallel, showing that diet has no

effect on either the date of beginning of Period III or the course of epidermization. The difference between the two curves gives the area of the epithelium.

In Fig. 4 an average curve is given for all four diets (Sets I and II), showing the course of all four periods of wound healing. It shows that contraction continues all through the period of epidermization and even for five days after the wound is completely healed. At this point the formation of pigment begins at the outside edge of the scar and as the pigmentation moves inward the scar rapidly enlarges until the pigmentation is complete, when it reaches a stationary state.

It would be interesting to compare this fourth period in animals with different degrees of pigmentation and determine the exact relationship between the formation of pigment and the scar area. Carrel³ says that the expansion of the cicatrix after the wound is healed is less marked in man than in the

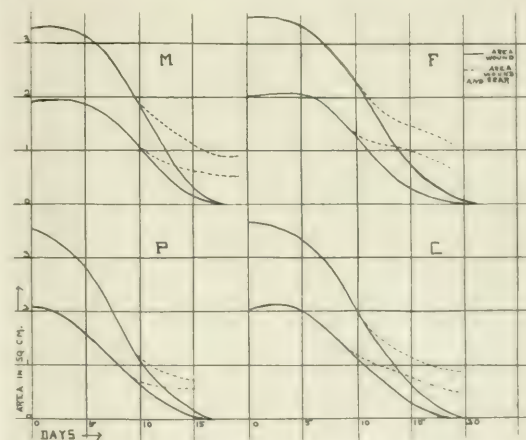


FIG. 5.—Results of Sets I and II Averaged Separately for Large and Small Wounds.

Curve M = mixed diet.

Curve C = carbohydrate diet.

Curve P = protein diet.

Curve F = fat diet.

Abscissæ = time in days; ordinates = wound area in sq. cm.

dog. If the expansion is conditioned by the formation of the pigment this would naturally result.

II. *Effect of Size of Wounds on Cicatrization.*—Carrel⁴ has already shown that the rate of contraction is proportional to the size of the wound, but that the rate of decrease is less rapidly than the area, so that large and small wounds tend to become equal. Fig. 5 shows the results in Sets I and II averaged for large and small wounds separately for all four diets. In every case the curves show that the rate of healing in large wounds is greater, so that the wounds heal in the same length of time. The rate of healing as measured by the change in area per day is not, however, proportional to the size of the wound at any one time. For example, take

Fig. 5 (C). The area of the small wound is 2 sq. cm. on the fifth day. At this time the rate of healing is .10 sq. cm. per day. The area of the large wound is 2 sq. cm. on the tenth day when the rate of healing is .35 sq. cm. a day. However, if the rates throughout each set of curves are compared it will be found that the ratio

$$\frac{\text{rate of healing of large wounds}}{\text{rate of healing of small wounds}}$$

on any given day is approximately equal to the ratio

$$\frac{\text{original size of large wounds}}{\text{original size of small wounds}}$$

if the quiescent period is neglected (see Table I). So that, knowing the rate of healing of a wound of any given size, the rate of healing of a wound of any other size can be calculated. However, this probably would hold true only within certain limits of the original size. In these experiments the wounds are all relatively small.

TABLE I

Day	S_1 = original size large wounds S_2 = original size small wounds	R_1 Rate healing small wounds in square cm. large wounds per day	R_2 Rate healing small wounds in square cm. large wounds per day	$S_1 = R_1$ $S_2 = R_2$
M 3-6	1.7	.04	.11	.07
6-9		.16	.30	.27
9-12		.20	.33	.34
12-15		.13	.23	.22
P 3-6	1.7	.08	.13	.14
6-9		.16	.23	.27
9-12		.20	.40	.34
12-15		.15	.23	.25
C 3-6	1.8	.07	.12	.12
6-9		.20	.30	.36
9-12		.17	.32	.31
12-15		.17	.23	.31
F 3-6	1.7	0	.08	0
6-9		.36	.52	.61
9-12		.26	.33	.44
12-15		.10	.17	.17

The results for F are poor, but for the others are fairly good. If this fact has any general application and can be extended to the interpretation of wounds of any size it would mean that the rate of contraction is governed by a variable factor depending on its age and a constant factor depending on the original size.

In comparing the curves for different diets in Fig. 5 it is seen that the effect of the diet on the length of the quiescent period is greater in the small than in the large wounds.

Neither the diet nor the size of wounds has any effect on the time of beginning of Period III. The formation of the epithelium starts about the ninth or tenth day in every case. The amount of contraction subsequent to this depends on the size of the wound when the epidermization begins. The contraction and epidermization complete the healing together. The size of the scar when complete healing has taken place is about the same in every case, and equals approximately one-quarter the size of the original wound.

DISCUSSION

In connection with these results it is interesting to consider the well-known fact that the ingestion of proteins produces a much greater increase in body metabolism than that of any other foodstuffs. In a recent monograph on the subject of the stimulating effects of nutrients, Benedict and Carpenter⁵ have given a very complete report of this question. They find that while carbohydrates give a maximum increment to the metabolism of 25 per cent and fats 12 per cent, this increment occurs within two hours and the metabolism then returns rapidly to the base line. With proteins the increment reached a maximum of 25 per cent to 45 per cent and persisted for as long as 8 to 12 hours. This increase in metabolism, or excess energy given off by the body as a result of the ingestion of food, may be regarded as waste energy, but Benedict suggests that we may consider the extra heat developed under these conditions as a normal physiological stimulus to cellular activity. Practical experience with heavy muscular work on protein and carbohydrate diets points to this conclusion and the results reported here would certainly support the idea that proteins have a specific influence in stimulating the whole cellular system to greater activity.

CONCLUSIONS

The length of the quiescent period of wound healing is affected by the diet. It varies from zero in protein-fed dogs to six days in the fat-fed animals. This variation in the quiescent period is more marked in smaller wounds. As a consequence, the date of final healing differs by about five days for the protein- and fat-fed dogs.

When the second period, or period of contraction, has set in the rate of contraction is not affected by the diet. It is governed by a variable factor depending on the age of the wound and by a constant factor proportional to the original size—

$$R_1 = \frac{S_1}{S_2} \text{ when } R_1 \text{ and } R_2 = \text{rates of healing of large and small wounds and } S_1 \text{ and } S_2 = \text{original areas of these wounds.}$$

The beginning of Period III, the period of epidermization, is independent of the size of the wound and the diet. It is determined by the age of the wound. Contraction and epidermization continue together until the wound is entirely healed.

After the wound is healed the scar continues to contract until pigmentation sets in. During this latter process it enlarges and reaches a stationary state after pigmentation is complete.

REFERENCES

1. Hooper, C. W., and G. H. Whipple: *Amer. Jour. Physiol.*, 1918, XLV, 573, 576.
2. Carrel, A.: *Jour. A. M. A.*, 1910, LV, 2148.
3. Carrel, A., and A. Hartman: *Jour. Exp. Med.*, 1916, XXIV, 429.
4. Du Noüy, P. L.: *Jour. Exp. Med.*, 1916, XXIV, 451; 1917, XXV, 721.
5. Benedict, F. G., and T. M. Carpenter: *Food Ingestion and Energy Transformation*. Carnegie Inst., Wash., 1918.

THE RELATION OF SPONTANEOUS NEPHRITIS OF RABBITS TO EXPERIMENTAL LESIONS*

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During the past few years an extensive literature has accumulated, dealing with the experimental production of renal lesions. A variety of injurious agents has been employed, among which may be mentioned cytotoxic sera,¹ cantharidin,² foreign proteins,³ uranium nitrate,⁴ bichloride of mercury,⁵ tartrates,⁶ diphtheria toxin,⁷ anesthetics,⁸ and a variety of bacteria, such as streptococci,⁹ staphylococci,¹⁰ colon bacilli,¹¹ Friedländer bacilli,¹² and others. Although lesions of various types have been obtained, many of them specific of the particular poison employed, it has not been possible adequately to reproduce a condition corresponding clinically or anatomically with advanced types of chronic nephritis in man. The work of Faber,¹³ who was able to produce arthritis in rabbits with great constancy by injecting streptococci intravenously some time after a preliminary intra-articular sensitizing inoculation with the same organism, suggested the employment of a similar procedure in the attempt to produce experimental nephritis. It was thought that a preliminary injection of bacteria in relatively high concentration directly into the renal artery might sensitize the kidney in such a way that subsequent small repeated intravenous injections might result in renal lesions of a chronic type. Coulter and Pappenheimer¹⁴ employed a somewhat similar method. Working with rabbits, they gave a series of intravenous injections of an extract of typhoid bacilli, and two weeks later injected the same material directly into the renal artery. To avoid possible confusion with "spontaneous lesions," attention was confined to the acute lesions, and the animals were killed after 48 hours. Scattered focal glomerular lesions, similar to those described in bacterial endocarditis, were found. In the unsensitized animals these changes were either very slight or absent.

The following experiments are reported because they represent an attempt to produce chronic renal disease by a method different from those previously used, and because it was possible accurately to control the significance of "spontaneous lesions" by direct inspection of the kidney at the beginning of the experiment, as well as by later examination at autopsy.

METHODS

Healthy rabbits weighing from 1000 to 2500 gm. were used. After a preliminary urine examination,[†] the animal was anesthetized with ether and the left kidney delivered through a lumbar incision. The vessels were stripped free of fat and connective tissue and the bacterial suspension was injected

into the renal artery through a fine needle. During the injection the kidney became mottled or blanched, but the normal color promptly returned. Bleeding from the punctured artery was slight, and stopped when the kidney was put back into the abdominal cavity. The wounds were closed with catgut and healed by first intention. In a few instances total or partial infarction of the kidney resulted from an arterial thrombus, but in most cases at autopsy the vessels were patent and there were no gross signs of circulatory disturbance.

After two weeks a series of intravenous injections was begun with the organism previously used. The size of the dose and the interval between injections varied with the animal's reaction. The injections were regulated in such a way that the animals lost weight and seemed ill. In different experiments from 1 to 19 re-inoculations were made over periods varying up to 15 months. Frequent urine examinations were made throughout the experiment, and in a few cases thallem tests were done.

Most of the animals died of cachexia and toxemia; the remainder were sacrificed. Gross specimens were preserved, and blocks were fixed in formalin, embedded in paraffin, cut, and stained with hematoxylin and eosin.

Six strains of streptococci were used; strains Q and Y were avirulent, long-chained green streptococci isolated from urine; strains T and S were hemolytic varieties obtained from septic infections and were highly virulent for rabbits; strains A and R, isolated from the throats of scarlet fever patients, were markedly hemolytic and virulent for rabbits. In the initial injections into the renal artery from 0.5 to 1.0 c. c. of a thick saline suspension of organisms grown for 24 hours in meat infusion broth and killed by heating for half an hour at 60 to 70° was used. The character of the emulsion was such that most of the bacteria were filtered out by the kidney. This was controlled by microscopic examination of a few kidneys removed shortly after the injection. Living 24-hour cultures were employed in the intravenous reinjections.

EXPERIMENTS

A single protocol of a typical experiment is given in detail in Table I; the remainder are summarized in Table II.

TABLE I. DETAILED PROTOCOL OF A COMPLETE EXPERIMENT

No. 51. White male rabbit

March 1, 1916. Weight 1580 gm. Urine clear.

March 2. Left kidney exposed through lumbar incision. It is of normal size and consistency, but there are many shallow depressions on the surface, varying in size up to 2 mm. in diameter. Growth from 0.5 c. c. broth (24-hour) of strain S (killed) injected into renal artery. During injection, yellowish blotches appeared over entire kidney, except the lower pole and anterior surface.

* These experiments were carried out during the winter of 1915-1916, at the suggestion of and in collaboration with Dr. Theodore Janeway. Publication has been unavoidably delayed.

† The urine was obtained by massaging the abdomen over the bladder.

March 3.	Animal in good condition. Urine contains albumin, granular casts and a few R. B. C.	
March 4.	Urine clear.	
March 6.	Urine clear. Weight 1550 gm.	
March 16.	Growth from 1/20 c. c. 24-hour broth culture strain S (living) intravenously.	
March 17.	Urine clear. 1/20 c. c. (S) intravenously.	
March 18.	Looks sick. 1/10 c. c. (S) intravenously.	
March 20.	Urine clear. 1/10 c. c. (S) intravenously.	1490 gm.
March 22.	Urine clear. 1/10 c. c. (S) intravenously.	1450 gm.
March 27.		1430 gm.
March 28.	1/20 c. c. (S) intravenously.	
March 30.		1350 gm.
April 5.	Urine clear.	1390 gm.
April 8.	Urine clear. 1/100 c. c. (S) intravenously.	1470 gm.
April 10.	Urine clear. 1/100 c. c. (S) intravenously.	1490 gm.
April 11.		1450 gm.
April 12.	1/100 c. c. (S) intravenously.	
April 17.	1/100 c. c. (S) intravenously.	
April 19.		1400 gm.
April 22.	1/100 c. c. (S) intravenously.	
April 24.		1350 gm.
April 25.	1/100 c. c. (S) intravenously.	
April 28.	1/100 c. c. (S) intravenously.	1300 gm.
May 2.	Urine clear. 1/100 c. c. (S) intravenously.	
May 3.	Urine clear.	
May 6.	1/100 c. c. (S) intravenously.	1350 gm.
May 9.	1/100 c. c. (S) intravenously.	1320 gm.
May 11.	1/100 c. c. (S) intravenously.	
May 14.	Urine clear. 1/100 c. c. (S) intravenously.	1300 gm.
May 15.	Animal killed. Autopsy: General condition good. A few parasitic cysts of omentum. Heart and lungs normal.	

Left kidney: Weight 5.0 gm. It is loosely adherent to region of scar without new formation of vessels. Capsule moderately thickened (post-operative), but strips freely. Same degree of surface pitting as seen at operation. Consistency seems normal. Cortex of normal width, markings distinct. Glomeruli appear as red dots. Intermediate zone separated from cortex by an irregular, grayish-yellow line about 1 mm. in thickness. Medulla rather pale. *Microscopically*: A good many small scattered areas of round-cell infiltration are seen. In some places there is a beginning fibrosis which causes the cortical depressions. The lesions are focal and interstitial. The glomeruli look normal. The vessels and tubules are normal except where involved in the scars.

Right kidney: Weight 5.0 gm. Gross and histological examination similar to that of left; same degree of scarring.

Renal vessels patent on both sides.

RESULTS

Apart from the "spontaneous nephritis" described below, no definite lesions were found. The glomerular, tubular, vascular and interstitial structures differed in no way from those of untreated controls. This result was unexpected in view of the direct and intensive injury, the constitutional reaction of the animals and the evidence of at least transient renal irritation furnished by the appearance of albumin, casts or blood in the urine after some of the injections. Pappenheimer, Hyman and Zedman¹⁸ studied rabbits' kidneys removed at short intervals after the injection of streptococci into the renal artery. They found that the organisms were rapidly disposed of by leucocytic and fixed cell phagocytosis, with return of the glomerulus to normal. An overwhelming bacterial injury, on the other hand, led to immediate partial or complete disorgani-

zation of the glomerulus by thrombotic or suppurative processes. This is possibly the explanation of the difficulty of producing experimentally a gradually progressive process such as that seen in the subacute or chronic glomerulonephritis of man. In our animals, despite repeated injections, the immediate injury was apparently promptly repaired without the initiation of an advancing lesion.

SPONTANEOUS NEPHRITIS

In connection with attempts to produce experimental nephritis, many writers refer to the difficulty of interpreting lesions which occur spontaneously in the kidneys of various animals, such as the rat,¹⁹ dog²⁰ and rabbit. Spontaneous rabbit nephritis has been recently described by Le Count and Jackson,²¹ who summarize the literature on the subject. Such lesions were found in many of our animals and correspond with those pictured in previous reports (Figs. 1-10).

Every grade of change from accumulations of a few round cells between the tubules to extensive scars was seen in one or another of the specimens. On gross examination, the earliest forms of lesion appear on section as streaks about 1 mm. wide, slightly more yellowish than the normal kidney substance running from the base of the intermediate zone to the surface. At this stage there is no corresponding depression on the cortical surface, but the lesion is shown by a mottling of the kidney over it. With more advanced disease there are very slight depressions, and in extreme cases a coarse pitting which may affect the entire renal surface. These depressions vary in size from minute dents up to pits 2 or 3 mm. in diameter.

Microscopically, the earliest lesions appear as collections of a few round cells in the interstitial tissues between the tubules. The latter show granular degenerations and the cell boundaries and the nuclei become indistinct. Later the remains of the tubules may be seen between dense collections of round cells. The next stages show the presence of new connective tissue, which finally may take the form of scars which contract and distort the tissues. The tubules may be greatly dilated and contain detritus or casts. The glomeruli, as a rule, show relatively little apparent change, even when the intervening tissue has been largely destroyed. In some cases there is marked fibrosis about the capsule, but the glomerular structure shows no definite alteration. Finally, the glomeruli may also disappear in the scar. The individual lesions may be large or small, they may be abundant or widely scattered, and they are located in cortex or in medulla. They are always distinctly focal, however, with normal intervening tissue, and are never diffuse, as in the contracted kidney of human nephritis. It seems probable that the lesion is a reaction to an injury which is not primarily interstitial.

In reviewing the reports on experimental rabbit nephritis, it is striking that many of the lesions described correspond in detail with these spontaneous lesions, thus raising the question of possible misinterpretation of the findings. An attempt was made in these experiments to control the significance of these lesions by careful inspection of the kidney for scars at

the beginning of the experiment when the renal artery was injected, comparing its appearance with the later autopsy findings. It was also possible to compare the left kidney, which was directly treated with a large dose of bacteria, with the right, which was affected only by the smaller intravenous reinjections. These findings are summarized in Table III.

In all but four of the 16 animals the appearance of the kidney at the end of the experiment was exactly like that seen

at the preliminary operation. In these four animals, periods of 161, 257, 352 and 460 days had elapsed since the beginning of the experiment, so that it is probable that the slight focal lesions which were similar to those seen in untreated controls had developed spontaneously. The duration of the other 12 experiments varied from 8 to 74 days. In all of these animals in which the kidney had been smooth at the start no lesions were found later at autopsy, and where the kidney had

TABLE II.—SUMMARY OF RESULTS OF EXPERIMENTS

No.	Description	Procedure	Remarks	Autopsy	No.	Description	Procedure	Remarks	Autopsy
11	Brown female. Weight 1250 gm.	Dec. 8, 1915. Injection into left renal artery of growth from 5 c. c. of broth in 0.5 c. c. salt sol. of strain Y (killed). Dec. 20, 1915-Mar. 13, 1917. Six intravenous injections of strain Y (living).	Occasional trace of albumin in urine after injections. Condition good except for loss of weight after injections.	Killed Mar. 13, 1917, 490 days from beginning of experiment. Both kidneys look normal except for few slight surface depressions. Microscopically: Normal except for moderate spontaneous lesions (p. 13).	56	Brown female. Weight 1250 gm.	Mar. 29, 1916. Injection into left renal artery of growth from 25 c. c. broth in 0.5 c. c. salt sol. of strain S (killed). Apr. 4, 1916-May 4, 1916. 15 intravenous injections of strain S (living).	Steady loss of weight.	Killed May 15, 1916, 55 days from beginning of experiment. Both kidneys normal in every way.
14	Brown male. Weight 2340 gm.	Dec. 13, 1915. Injection into left renal artery of growth from 5 c. c. broth in 0.5 c. c. salt sol. of strain Y (killed). Dec. 24, 1915-Feb. 8, 1916. Six intravenous injections of strain Y (living).	Albumin in urine at times after the injections. Moderate loss of weight.	Killed Feb. 8, 1916, 61 days from beginning of experiment. Right kidney normal. In left kidney except for lower pole. Microscopically: No lesions except the infarct.	57	Brown female. Weight 1020 gm.	Mar. 20, 1916. Injection into left renal artery of growth from 25 c. c. broth in 0.5 c. c. salt sol. of strain S (killed). Apr. 4, 1916-Aug. 29, 1916. 15 intravenous injections of strain S (living).	Steady loss of weight.	Died Aug. 24, 1916, 161 days from beginning of experiment. Slight spontaneous lesions in both kidneys.
15	White male. Weight 1420 gm.	Dec. 14, 1915. Injection into left renal artery of growth from 1 c. c. broth in 0.5 c. c. salt sol. of strain Y (killed). Dec. 27, 1915-Jan. 28, 1916. Five intravenous injections of strain Y (living).	Steady loss of weight.	Died Jan. 29, 1916, 44 days from beginning of experiment. Both kidneys normal microscopically.	59	Brown female. Weight 1290 gm.	Mar. 20, 1916. Injection into left renal artery of growth from 25 c. c. broth in 0.5 c. c. salt sol. of strain S (killed). Apr. 4, 1916-Mar. 7, 1917. 16 intravenous injections of strain S (living).	Loss of weight after injections, with occasional albuminuria.	Died Mar. 7, 1917, 359 days from beginning of experiment. Minimal degree of spontaneous lesion. Kidneys otherwise normal.
16	Black male. Weight 1600 gm.	Dec. 14, 1915. Injection into left renal artery of growth from 5 c. c. broth in 0.5 c. c. salt sol. of strain Y (killed). Dec. 27, 1915-Aug. 29, 1916. Seven intravenous injections of strain Y (living).	Loss of weight after each injection. Sixty eight injections. Albumin and R. B. C. in urine for two days.	Killed Aug. 29, 1916, 257 days from beginning of experiment. Both kidneys normal in gross and microscopically, except for a small focus of spontaneous nephritis.	63	Male. Weight 1030 gm.	Mar. 25, 1916. Injection into left renal artery of growth from 25 c. c. broth in 0.5 c. c. salt sol. of strain R (killed). Apr. 8, 1916-June 15, 1916. 14 intravenous injections of strain R (living).	Steady loss of weight.	Died June 15, 1916, 71 days from beginning of experiment. Kidneys normal in every way.
17	Brown hare. Weight 1500 gm.	Dec. 22, 1915. Injection into left renal artery of growth from 3 c. c. broth in 0.5 c. c. salt sol. of strain T (killed). Jan. 5, 1916-Jan. 22, 1916. Three intravenous injections of strain T (living).	Steady loss of weight. Albumin and casts in urine for five days after last injection.	Died Jan. 22, 1916, 31 days from beginning of experiment. Both kidneys normal microscopically.	65	Male. Weight 1690 gm.	Apr. 1, 1916. Injection into left renal artery of growth from 25 c. c. broth in 0.5 c. c. salt sol. of strain R (killed). Apr. 15, 1916-May 19, 1916. 10 intravenous injections of strain R (living).	Steady loss of weight. Developed arthritis of left hind leg.	Died May 19, 1916, 49 days from beginning of experiment. Kidneys normal in gross and microscopically.
19	Brown hare. Weight 1650 gm.	Dec. 22, 1915. Injection into left renal artery of growth from 3 c. c. broth in 0.5 c. c. salt sol. of strain T (killed). Jan. 5, 1916-Jan. 22, 1916. Three intravenous injections of strain T (living).	Steady loss of weight. Albumin after first injection. Albumin, casts and R. B. C. for one day after fourth injection.	Died Jan. 22, 1916, 31 days from beginning of experiment. Both kidneys show marked spontaneous interstitial lesions. Otherwise normal in gross and microscopically.	66	Male. Weight 1100 gm.	Apr. 1, 1916. Injection into left renal artery of growth from 0.5 c. c. broth in 0.5 c. c. salt sol. of strain R (killed). Apr. 15, 1916-June 1, 1916. 12 intravenous injections of strain R (living).	Steady loss of weight.	Died June 5, 1916, 66 days from beginning of experiment. Kidneys normal except for a few small spots of spontaneous nephritis.
31	White male. Weight 1580 gm.	Mar. 2, 1916. Injection into left renal artery of growth from 0.5 c. c. broth in 0.5 c. c. salt sol. of strain S (killed). Mar. 16, 1916-May 14, 1916. 17 intravenous injections of strain S (living).	Steady loss of weight.	Killed May 15, 1916, 55 days from beginning of experiment. Both kidneys are grossly and microscopically normal. Otherwise normal.	12	Brown female. Weight 1550 gm.	Dec. 9, 1915. Injection into left renal artery of growth from 5 c. c. broth in 0.5 c. c. salt sol. of strain S (killed). Dec. 29, 1916. One intravenous injection of strain S (living).	Rapid emaciation. Albumin and casts in urine for two weeks after last injection.	Died Dec. 13, 1916, 14 days from beginning of experiment. Both kidneys normal in gross and microscopically.
53	White male. Weight 1570 gm.	Mar. 2, 1916. Injection into left renal artery of growth from 0.5 c. c. broth in 0.5 c. c. salt sol. of strain S (killed). Mar. 16, 1916-May 14, 1916. 17 intravenous injections of strain S (living).	Steady loss of weight. Transient albuminuria followed some injections.	Killed May 16, 1916, 54 days from beginning of experiment. Both kidneys show marked gross and microscopically interstitial lesions. Otherwise normal.	77	Male. Weight 1570 gm.	Apr. 27, 1916. Injection into left renal artery of growth from 0.5 c. c. broth in 0.5 c. c. salt sol. of strain S (killed). Apr. 27, 1916-May 14, 1916. 17 intravenous injections of strain S (living).	Steady loss of weight.	Died May 5, 1916, eight days from beginning of experiment. Extensive spontaneous lesions.

been pitted at the start, focal interstitial lesions were found. Furthermore, in spite of the intensive direct treatment of the left kidney, in every case in which changes were present they were of equal extent in the two kidneys. It seems impossible to interpret these findings in any other way than that all these lesions were spontaneous and independent of the experimental procedure. The great frequency and variety of the changes, their apparent independence of any constant factor in the animal's condition, such as age, weight, etc., suggest that possibly many of the chronic interstitial lesions ascribed in the literature to experimental infection are really the effects of spontaneous nephritis.

TABLE III.—SPONTANEOUS LESIONS

COMPARISON OF APPEARANCE OF LEFT KIDNEY AT OPERATION WITH LESIONS FOUND LATER AT AUTOPSY

No.	Description	Appearance of left kidney at beginning of experiment at operation	No. days to autopsy	Lesions at autopsy		No.	Description	Appearance of left kidney at beginning of experiment at operation	No. days to autopsy	Lesions at autopsy	
				Right kidney	Left kidney					Right kidney	Left kidney
11	Brown female. Weight 1560 gm.	Normal size and appearance; surface smooth.	460	Weight 8 gm. Looks normal except for slight cortical depressions. Capsule not adherent. <i>Microscopically</i> : Moderate number of linear interstitial lesions, moderately advanced. A few small, scattered, round-cell infiltrations.	Weight 8 gm. Looks normal except for some thickening of capsule (post-operative). Capsule strips freely. A few slight cortical depressions (<i>less than on right</i>). <i>Microscopically</i> : Same as right.	53	White male. Weight 1450 gm.	Numerous markedly depressed scars over surface.	74	Weight 5 gm. Very many marked cortical depressions. Capsule strips freely. <i>Microscopically</i> : Many well-advanced lesions, with fibrosis, contracted scars, compression and atrophy of glomeruli and tubules. Apart from these focal interstitial lesions, kidney is normal.	Weight 5 gm. Post-operative capsular thickening. Similar lesions to those on right and of same degree.
14	Brown male. Weight 2510 gm.	Normal size and appearance; surface smooth.	61	Weight 8.5 gm. Looks perfectly normal. Capsule not adherent. <i>Microscopically</i> : No lesions.	Total infarct of kidney except for lower pole. Microscopic sections of lower pole show normal kidney.	56	Brown female. Weight 1250 gm.	Normal.	55	Weight 4 gm. Normal in gross and microscopically.	Weight 4 gm. Like right except for post-operative capsular thickening.
15	White male. Weight 1429 gm.	Normal size and appearance; surface smooth.	44	Weight 4+ gm. Looks normal; surface smooth. Capsule not adherent. <i>Microscopically</i> : No lesions seen.	Weight 4+ gm. Some post-operative thickening of capsule; strips freely. <i>Microscopically</i> : No lesions seen.	57	Brown female. Weight 1020 gm.	Surface perfectly smooth.	161	Weight 5 gm. A very few very slight depressions on surface. Capsule strips freely. <i>Microscopically</i> : A few round-cell infiltrations with beginning fibrosis.	Weight 5 gm. Same as right except for post-operative capsular thickening.
16	Black male. Weight 1660 gm.	Normal size and appearance; surface smooth.	257	Weight 5.5 gm. Capsule strips freely. A very few small "pits" on surface; in general, is a smooth kidney. <i>Microscopically</i> : Two small round-cell accumulations with beginning fibrosis in entire section of the cortex.	Weight 6+ gm. Post-operative capsular thickening; strips freely. No "pits" seen. <i>Microscopically</i> : One lesion seen in entire section, similar to right.	59	Brown female. Weight 1290 gm.	Surface perfectly smooth.	352	Weight 5 gm. A very few scattered slight beginning surface depressions. <i>Microscopically</i> : No abnormality seen in several sections.	Weight 5 gm. Same as right except for post-operative capsular thickening.
17	Brown hare. Weight 1990 gm.	Normal size and appearance; surface smooth.	31	Weight 5.0 gm. Capsule strips freely. Surface smooth. Normal in gross and microscopically.	Weight 5.5 gm. Post-operative thickening of capsule; strips freely. Normal in gross and microscopically.	63	Male. Weight 1030 gm.	Surface perfectly smooth.	71	Weight 4.5 gm. Normal in gross and microscopically.	Weight 5.5 gm. Like right except for post-operative capsular adhesions.
19	Brown hare. Weight 1650 gm.	Kidney shows multiple depressed areas on surface, 1 to 1.5 mm. in diameter.	32	Weight 6.5 gm. Multiple small depressions on surface, but capsule strips freely. <i>Microscopically</i> : Abundant, well-advanced, scattered interstitial lesions, both in cortex and medulla, with extensive round-cell infiltration, fibrosis, and compression and atrophy of tubules.	Weight 7.5 gm. Post-operative thickening of capsule; strips freely. Similar lesions to those on right and of same degree.	65	Male. Weight 1090 gm.	Surface perfectly smooth.	40	Weight 5 gm. Normal in gross and microscopically.	Weight 5+ gm. Like right except for post-operative capsular adhesions.
51	White male. Weight 1380 gm.	Many small, depressed scars over kidney surface.	73	Weight 5 gm. Multiple small depressions on surface, but capsule strips freely. <i>Microscopically</i> : A good many small accumulations of round cells with beginning fibrosis. Kidney otherwise normal.	Weight 5 gm. Post-operative thickening of capsule; strips freely. Similar lesions to those on right and of same degree.	66	Male. Weight 1110 gm.	Surface perfectly smooth.	66	Weight 5 gm. Surface smooth and normal. <i>Microscopically</i> : A very few small, scattered, round-cell infiltrations.	Weight 5 gm. Like right except for post-operative capsular thickening.
						12	Brown female. Weight 1550 gm.	Surface perfectly smooth.	14	Weight 4.5 gm. Normal in gross and microscopically.	Weight 4.5+ gm. Like right except for post-operative capsular thickening.
						77	Male. Weight 1270 gm.	Extreme pitting of kidney surface.	8	Weight 6.0 gm. Extreme pitting of kidney surface, but capsule strips freely. <i>Microscopically</i> : The sections are shot with numerous contracted scars which distort the kidney structure. Areas of compressed or dilated tubules containing casts. The most extreme grade of spontaneous lesion.	Weight 4.5 gm. Same kind and degree of lesions as on right.

CONCLUSIONS

1. An attempt was made to produce chronic nephritis in rabbits by intravenous injections of streptococci, following a direct injection into the renal artery.
2. Failure to produce chronic glomerular lesions was thought to be due to the means used by the kidney to dispose of injected organisms, which resulted in complete healing if the glomerulus survived the acute injury.
3. Chronic focal lesions were found in many animals.
4. Control examinations of the kidney at the beginning of the experiment, and comparison of differently treated right

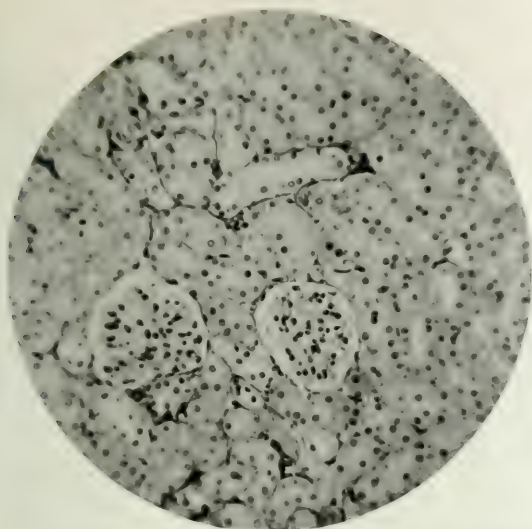


FIG. 1.—Earliest type of lesion. Shows beginning accumulation of round cells between the tubules.

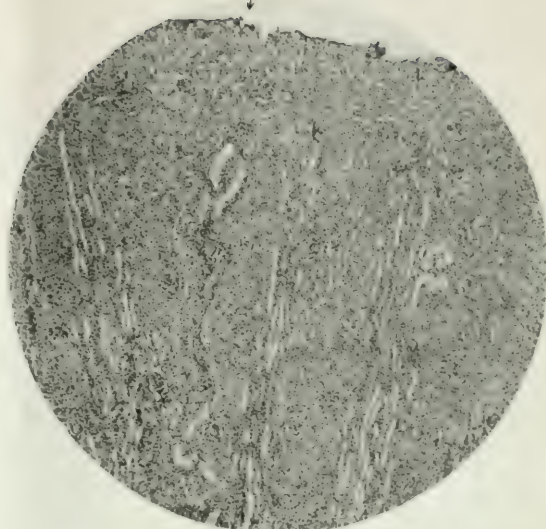


FIG. 2.—Earliest type of lesion appearing as a linear streak of round-cell infiltration.

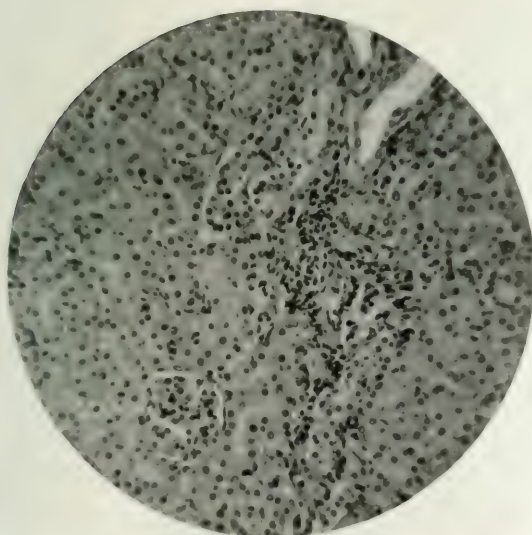


FIG. 3.—Portion of Fig. 2. High power. Shows round-cell infiltration with beginning tubular changes.



FIG. 4.—Moderately advanced lesion.

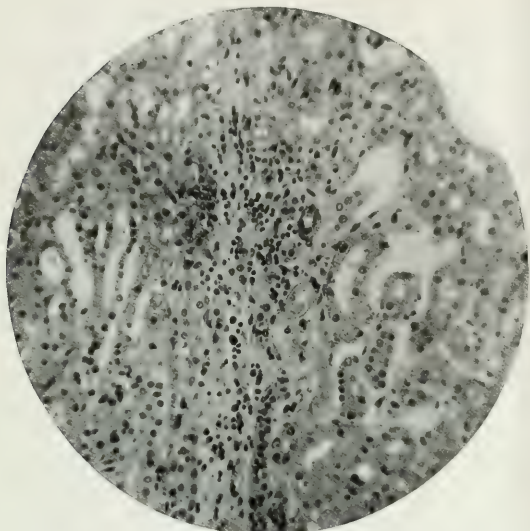


FIG. 5.—Portion of Fig. 4. High power. Beginning scar with shrunken and distorted tubules.

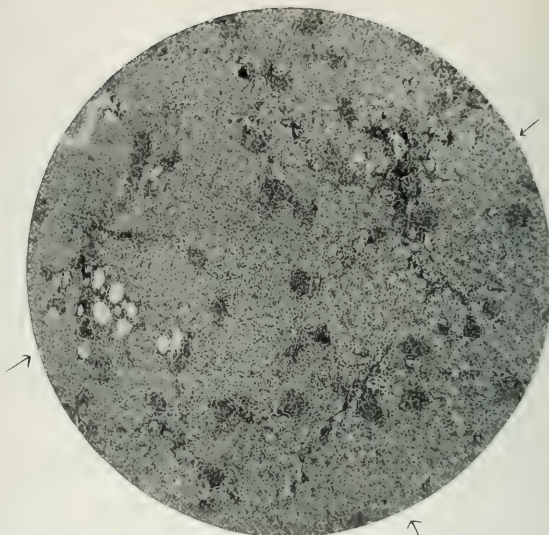


FIG. 6.—Multiple small areas of scarring with normal intervening tissue. Well-advanced lesion.

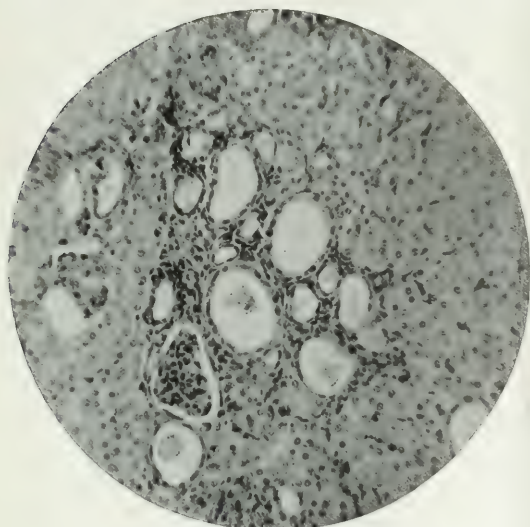


FIG. 7.—Same as Fig. 6. High power. Shows area of fibrosis with atrophied dilated tubules and fibrosis around a glomerulus.

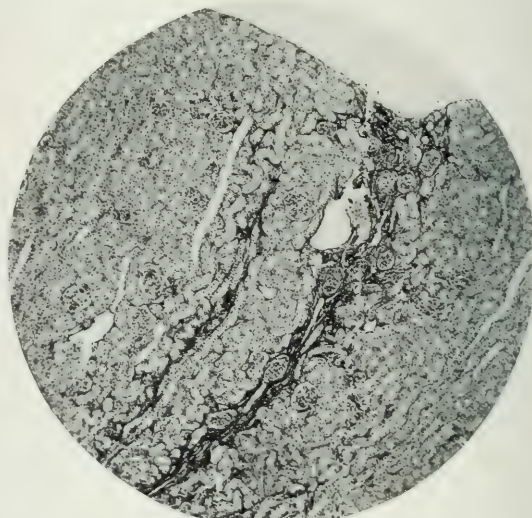


FIG. 8.—Very advanced lesion showing a linear scar with destruction of normal elements.



FIG. 9.—Low power. Most advanced type of lesion, resulting in a scar.

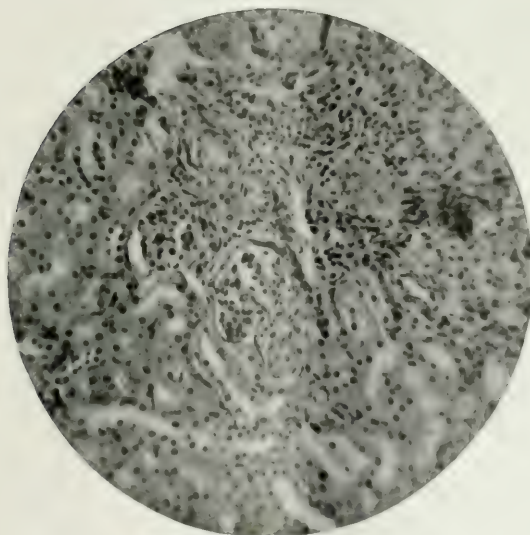


FIG. 10.—Portion of Fig. 9. High power.



and left kidneys suggest that all these lesions represented the "spontaneous nephritis of rabbits."

REFERENCES

1. Pearce, Richard M., and Elsenbrey, A. B.: A physiological study of experimental nephritis due to bacterial poisons and cytotoxic sera. *Jour. Exp. Med.*, 1911, XIV, 306.
2. Ople, E. L.: Lymph formation and edema of the liver with experimental nephritis produced by cantharidin. *Jour. Exp. Med.*, 1912, XVI, 831.
3. Longcope, Warfield T.: The production, of experimental nephritis by repeated proteid intoxication. *Jour. Exp. Med.*, 1913, XVIII, 678.
4. Oliver, Jean: The histogenesis of chronic uranium nephritis, with especial reference to epithelial regeneration. *Jour. Exp. Med.*, 1915, XXI, 425.
5. MacNider, William de B.: A study of acute mercuric chlorid intoxications in the dog, with especial reference to the kidney injury. *Jour. Exp. Med.*, 1918, XXVII, 413.
6. Underhill, Frank P., Wells, H. Gideon, and Goldschmidt, Samuel: Tartrate nephritis. *Jour. Exp. Med.*, 1913, XVIII, 322.
7. Frothingham, Channing, Jr.: A glomerular and arterial lesion produced in rabbits' kidneys by diphtheria toxin. *Jour. Med. Res.*, 1914, XXX, 365.

8. MacNider, Wm. de B.: A study of the naturally nephropathic kidney of the dog rendered acutely nephropathic by uranium or by an anesthetic. Part 2. *Jour. Med. Res.*, 1916, XXXIV, 199.
9. Le Count, E. R., and Jackson, Lella: The renal changes in rabbits inoculated with streptococci. *Jour. Infec. Dis.*, 1914, XV, 389.
10. Major, Ralph H.: The production of kidney lesions with staphylococcus aureus toxins. *Jour. Med. Res.*, 1917, XXXV, 349.
11. Bailey, C. H.: Chronic nephritis in rabbits by repeated intravenous injections of living colon bacilli. *Jour. Exp. Med.*, 1916, XXIII, 773.
12. Major, Ralph H.: The production of acute and chronic kidney lesions with bacillus mucosus capsulatus. *Jour. Med. Res.*, 1917, XXXII, 125.
13. Faber, Harold K.: Experimental arthritis in the rabbit. *Jour. Exp. Med.*, 1915, XXII, 615.
14. Coulter, C. B., and Pappenheimer, A. M.: *Proc. New York Path. Soc.*, 1916, XVI, 80.
15. Pappenheimer, A. M., Hyman, H. T., and Zedman, F. D.: *Proc. New York Path. Soc.*, 1916, XVI, 73.
16. Ophüls, W., and McCoy, George W.: Spontaneous nephritis in wild rats. *Jour. Med. Res.*, 1912, XXVI, 249.
17. Winternitz, M. C., and Quinby, Wm. C.: Experimental nephropathy in the dog. *Jour. Urology*, 1917, I, 139.

A SKETCH OF DR. LYMAN SPALDING¹

By HENRY M. HURD, M. D.

Dr. Lyman Spalding was born at Cornish, N. H., in 1775. His early education was obtained at the Charlestown Academy, and later he was a student in the office of Dr. Nathan Smith, the eminent founder of medical schools, and the first of the name of the Smiths who later became distinguished in New England and Maryland. He afterwards visited the Harvard Medical School in 1794 and attended two courses of lectures there, but did not receive his degree of M. D. until 1797. He returned to Cornish, N. H., the residence of Dr. Smith, and took charge of his practice during the latter's absence in Europe. He subsequently taught chemistry and materia medica with Dr. Smith at the newly established medical school at Dartmouth College, N. H. He also became demonstrator of anatomy.

He soon removed to Walpole, N. H., where he practised for a few months also. His residence there is mainly interesting because of the fact that he purchased a set of Perkins Tractors, then much used and highly praised for the treatment of diseases. These tractors were sold for \$20.00, with the exclusive right to use them in practice both in this country and in Europe. It was one of the common medical frauds which are perpetrated on all nations about once in so often.

Dr. Spalding removed to Portsmouth, N. H., in 1797, and there had a successful career. He became a contract army surgeon, and had so much to do that he relinquished his connection with Dartmouth College. He was a diligent student, and active in all matters connected with medical co-operation.

He established a medical society, an anatomical museum, and originated and distributed so-called "Bills of Mortality," giving the causes of death of persons who died in Portsmouth from the years 1800-1813. He also essayed the growing of opium and lettuce in his garden for medicinal purposes.

In the "Life of Dr. Lyman Spalding" several interesting chapters are given on the introduction of vaccination into this country. Dr. Spalding, who was living at Portsmouth, wrote to Dr. Waterhouse, of Cambridge, who had received the Kine Pox from Jenner in England and seems to have had the monopoly of the introduction of vaccination into this country. Waterhouse was undoubtedly a man of ability and energy, but probably lacked money and felt the need of exploiting the new discovery for his own benefit. He, accordingly, writes to Dr. Spalding, in reply to his letter, asking for one-quarter of the amount received from Dr. Spalding's vaccinations during the succeeding 14 months, insists that "the small sum of five dollars" be charged for each vaccination, and guarantees that the exclusive privilege will be granted upon these terms. He also makes careful mention of the fact that he has Jenner's matter direct from England. A long correspondence took place between Spalding and Waterhouse. Both parties seem to have been anxious to make money from the introduction of vaccination, but Waterhouse appears in the most unfavorable light. After acceding to Spalding's proposition that he have exclusive control of vaccination in Portsmouth, he shows great anxiety that he, Spalding, should associate with him a Dr. Cutter and, later, Dr. Cutter's son, on the ground that the activity of these men would increase the number of vaccinations and thereby increase the profits to be

¹Read before The Johns Hopkins Hospital Historical Club, February 10, 1919.

derived from the exclusive privilege of managing them. In one letter Spalding asks for the privilege for 12 months, and later suggests that he will pay 10 per cent of all the sums which he receives for vaccination until such time as vaccination becomes public property. All that he received from Dr. Waterhouse seems to have been the exclusive privilege of vaccinating persons within the limits of Portsmouth, and a small piece of thread which had been dipped in the vaccine lymph. Later it seems that Spalding was to pay \$150.00 for this piece of thread, and a certain proportion of the money which he received for the vaccinations. Owing to the fact that it soon became apparent that one patient could be vaccinated directly from the arm of another, the exclusive privilege of using the vaccine lymph was soon broken up.

This destruction of the monopoly was undoubtedly much hastened by the unsatisfactory character of the vaccination when the thread impregnated with lymph was used, and the great inferiority of this method to the method of vaccinating from arm to arm. The physicians had many failures. It is also interesting to note that Dr. Spalding, on two separate occasions, made observations upon patients who had been vaccinated and afterwards placed in smallpox hospitals, and freely exposed to the disease for a number of days without acquiring smallpox. Spalding also received a letter from Edward Jenner, the discoverer of vaccination, and subsequently a specimen of vaccine lymph directly from him.

Spalding issued at Portsmouth during the following 12 years bills of mortality—so-called—beginning in the year 1801. Copies of these bills were sent to John Adams, then President of the United States, and subsequently to Thomas Jefferson, Benjamin Waterhouse and Benjamin Rush. Waterhouse, with his usual critical spirit, made reply in the following letter:

Cambridge, March 18, 1802. Dear Sir: Your letter of the 11th inst. came duly to hand and I have endeavored to comply with your request, so far as to send you some matter on the point of a quill. As to the thread, it is full a month old, but was from a very perfect case and has been kept in a proper degree of temperature ever since. I am now so in the habit of taking the vaccine fluid from arm to arm, that I am not so constant in preserving it on the thread or otherwise. Considerable attention and patience are required in the first use of an old thread. It ought always to be moistened with the vapor of hot water.

You mention my not having answered your last letter. I have received no letter from you since you wrote to me in answer to one of mine. I received a printed bill of mortality, 5 or 6 weeks ago, but no written line whatever with it and I have had no letter from you for 4, 5 or perhaps 6 months past.

I have just received "Observations on the Cow Pox" from Dr. Lettsom. I shall probably publish a second pamphlet in a month or so, being practical observations, etc. In the meantime I sent a few to the Medical "Repository" for their next number.

I am glad to find that you attend to the occurrences of Mortality. Excuse me for making a few remarks on the one you were so obliging to send to me. 1. Did APHTHAE kill the infant, or was it a symptom of another disorder, or in other words: was it sympathetic or IDIOPATHIC?

2dly. We very rarely see consumption in patients above 50 years of age, more rarely above sixty and very rarely indeed at 70.

There is a chronic cough and emaciation, and great expectoration in old people, but it is not the true Phthisis Pulmonalis.

3dly. Is not DEBAUCHERY rather a VAGUE term for a general Head? Does it mean Drunkenness exclusively?

4thly. I never yet saw a very young child with Epilepsy. There is a wide space indeed, between the convulsions of infants, and that truly wonderful disease, EPILEPSY.

5thly. Mortification: Was it in the bowels or the feet? As they are widely different in their cause. See Pott in the LATTER.

6thly. Death from SCROFULA is very uncommon. It predisposes to fatal diseases.

7thly. PAREGORIC: Does it mean that the Child was poisoned by that composition? If so, had it not better been by Opium as Paregoric means a Mitigator?

You will excuse these hasty observations that occurred on the perusal. They have not originated from a disposition to criticise but from a desire to have them free from every exception. Yours Steadily, B. WATERHOUSE.

In 1802 Spalding invented a galvanic battery, which gave rise to considerable correspondence, and which unquestionably was used extensively among his brother physicians. He had letters asking how to make similar batteries and also their exact therapeutic uses. He further devised a process for manufacturing oxygen for inhalation, and later invented a soda water fountain, which seems to have been quite extensively used. As he neglected to protect his invention by patents, as it appears in his biography some years later, patents were secured by other persons, and he was forbidden to use it without paying a royalty for his own invention. He was an active writer, especially upon anatomical and surgical subjects. His practice also extended in surgical lines, and he performed operations for hernia, extraction of cataract and removal of necrosed bone. He continued his interest in vaccination, and received a second letter from Jenner, who acknowledged the reception of some interesting details concerning vaccination and the bills of mortality, for which he thanked him. In Jenner's letter an interesting detail is given concerning the good effect of vaccination in controlling cases of smallpox in Vienna. Prior to vaccination the annual average of such cases was 800. Four years subsequent to the introduction of vaccination, but two cases of smallpox occurred in the city.

Dr. Spalding seems to have had a remarkable facility for friendship, and made warm friends in many parts of the country. One of his friends and subsequent correspondents was Bishop Philander Chase, a boyhood acquaintance, who subsequently became Bishop of Ohio, and later of Illinois and founder of Kenyon and Jubilee Colleges. Dr. Luther Jewett was another friend, a Vermont worthy who had excelled in the practice of medicine, the practice of law, the gospel ministry and the editorship of an influential newspaper; four distinct branches of effort, in each of which he achieved marked success. He was also a warm friend of Dr. John C. Warren, of Boston; Dr. Alexander Ramsay, the famous anatomist from Scotland, and Dr. George Shattuck, of Boston. He wrote letters to John Bell, the distinguished Edinburgh surgeon, and also to Charles Bell, and as his thoughts turned very much to medicine abroad, he made every effort to get an opportunity to visit England and the continent to better fit

himself to teach medicine. He sent a petition to the Secretary of State of the United States Government, asking that he be made a special messenger to carry dispatches to France, and received a courteous message to the effect that the services of no such messengers were needed at that time. He visited Philadelphia in order to fit himself better for his profession, and there saw the eminent Dr. Physick, and Drs. Wistar, Rush, Shippen and Barton. He writes that the school in Philadelphia had 350 medical students and later, when in New York, he contrasts the popularity of Philadelphia and the large number of students with the fact that New York had only about 100 medical students.

There is an interesting chapter in Spalding's life which has been detailed at considerable length by his biographer and deserves mention. In 1809 he became connected with the Fairfield Academy, located at Fairfield, about 10 miles from Little Falls, N. Y. Fairfield Academy was one of a chain of academies which had been established to promote education in the state under the charge of the Board of Regents. The great demand for medical men to provide for the needs of an ever increasing emigration to the west at this time gave rise to many medical schools. In addition to the New England schools founded by Dr. Nathan Smith, there were schools at Pittsfield, Mass., and Castleton, Vt., in addition to Harvard and the schools in Philadelphia and New York. He was appointed lecturer at Fairfield Academy in 1809, and lectured there for several years. The journey to Fairfield from Boston was a matter of three days and nights. He was made lecturer on chemistry and surgery during his first appointment, while Dr. George C. Shattuck, of Harvard, was made lecturer on medicine. The courses seem to have been not simultaneous, but tandem, as it were, Dr. Spalding lecturing on chemistry and surgery for six weeks, and being followed by Dr. Shattuck, who lectured for the same period on medicine, this making a term of three months. The success of the school was so great that it became necessary to erect a new building, and permission was asked of the legislature to establish a lottery to raise \$5000. Lotteries, it may be remarked, were at this time a popular method of raising money for educational and religious purposes. The Washington Monument in Baltimore was started by a lottery, as also the University of Maryland, the First Presbyterian Church and St. Paul's Church. Many details are given in the biography of Spalding in reference to the lottery plan, and new light is thrown upon it by the suggestion in one of the letters that, if the legislature granted the authority, the privilege of the lottery might be disposed of to some other parties at a discount. The success of the school at Fairfield became so great as to excite the cupidity of persons who were interested in the development of Hamilton Academy, at Clinton, N. Y., into Hamilton College, and an effort to establish a similar medical school at Hamilton. The agitation finally brought an appropriation of \$100,000 to Hamilton Academy, and it became Hamilton College, while Fairfield was obliged to be satisfied with receiving \$10,000 for the construction of a building and a charter giving the privilege to grant degrees, and thus to become an established medical school.

The following letter, sent by Dr. Spalding to Dr. George Shattuck, of Boston, gives a very interesting idea of his conception of the influence of medical teaching, and its benefit to the medical teacher:

Dear Sir— I can only say that I regret exceedingly the opinion of yourself and friends, that your avocations will not suffer you to visit Fairfield once more. I acknowledge that, at present, the compensation is not adequate to the output and the loss of business, but, Sir, I do really believe that this school may be made second to none but Philadelphia. If not, I will join with you in resignation. What effect has the Professorship already had on you? It has compelled you to pay close attention to your profession, to pass the whole of Cullen's "Nosology" in review, before you annually, and thereby qualifying you for the practice of your profession more than any other way in which you could have spent your time. It is the high road to fame, and usefulness. I know that my sacrifices have been great. I know that yours must be. But, show me the man who has risen to be a Prince of Physicians, while slumbering on the couch of idleness.

Soon after I came to Portsmouth, I resigned my office of Professor of Chemistry in Dartmouth, no doubt from the same motives that now influence you, with this addition, that my lectures there had to continue three months. I soon found myself slumbering on my oars and relaxing my pursuits. In fact, so far from improving, I hardly kept pace with the others. A kind of indifference for science pervaded me: Indignant I aroused, I went to Hanover to see Ramsay, I went to Philadelphia, and I planned a voyage to Europe. This change, Sir, I consider the most happy circumstance in my whole Professional career.

Admit that you resign your office. Man is an indolent animal. What inducement have you then, to labor incessantly? None! Your reputation is as high as that of your contemporaries. Then, wrapped in the lap of affluence and ease, you will slumber and sleep till old age creeps upon you, when you will find yourself outstripped in the race of usefulness and fame, your opinions so antiquated as to be regarded not, and yourself a mere old Granny!

Look at the Friars, or rather, Fathers of Physic. Who have they been or who are they now? So far as my memory serves me: Teachers of Physic. Boerhaave, Cullen, Desault. Look at Rush, Warren and Smith. What has put them at the head of the profession? Nothing but their being compelled to labor, and annually to review their profession, and incorporate with their old stock all the new improvements. Show me a man in private practice who does this, annually. He is not to be found. But, your friends say that you can do this, yet stay at home. I acknowledge this, but tell me honorably. Will you do it? No, Sir, you have no inducement. For a man to be pre-eminently great, there must be a great occasion. What made Washington Great? Opportunity. You are now on the same high road to reputation that every Prince of Physicians has travelled. If you turn aside, you are lost forever. These in conjunction with those in my last letter are the reasons which ought to influence you. You can have no doubt of my wishes on the subject. The time for the commencement of the lectures is so near at hand, that no successor can be appointed in season for the next course. I therefore beseech you, on my account, if neither honor nor fame will move you, to deliver This One Course, and I will consent to any arrangement that you may then choose to make. If nothing farther, as a mere matter of policy, I wish you to withhold your resignation till the meeting of the Trustees of the New Medical College and let us see what they will do for us.

Dr. Mann I knew had been appointed a Hospital Surgeon, but I did not know that he had been made Surgeon General. He must be with the Army by this time, and cannot be prepared for the ensuing course. I have no objection to this man, but must for want of room decline saying anything about your successor until I hear from you again. Your friend, Lyman Spalding.

Shattuck, after serving two terms as professor of medicine, relinquished the position, but Spalding, in 1813, was made president of the Fairfield College, and filled most of the chairs in 1814-1815 and 1816. The number of students seems to have varied between 50 and 70. Spalding seems to have done very faithful, conscientious work, for which he received somewhat irregular pay, and often more pay in promises than in actual money. The school remained in active operation until 1839, when it went to pieces in consequence of squabbles among the faculties as to the division of fees from medical students. The fees seem to have been very small.

In 1814, Spalding went to New York to reside, and had an office on Broadway, for which he was to pay about \$200 per year. His fees from his patients during the first year amounted to a little more than \$1000. At this time, Spalding seems to have attempted to write a book entitled the "Institutes of Medicine" which, as far as I can learn, was never published in book form, but was circulated in pamphlets, each chapter furnishing a pamphlet. It was praised by Shattuck and Waterhouse, and the reception of a sample pamphlet was certainly acknowledged even by Dr. Caldwell, but the book seems to have made little impression.

The following letter is from Governor Plumer, of New Hampshire, a friend of Spalding's:

Epping, N. H., Oct. 24, 1813. Dear Sir: This week I received your letter with your "Reflections on Fever," and Report of the Trustees of the Free Schools, for which you will please accept my grateful acknowledgments. I have read your pamphlet with attention and pleasure, but it is on a subject with which I am not sufficiently acquainted to decide with precision. You know the low state of the Faculty in New Hampshire. We have scarcely any who write on the subject of medicine, and of the great body of our country physicians but few who have any books to read, and what is worse they have little inclination to purchase books, to read those few that they have, or to investigate the complex and intricate subjects of their profession. These facts have long induced me to believe that, in many cases, the patient has more to apprehend from the ignorance of the physician, than from the disease, and that it is safer to trust to nature for a cure than to rely on the prescriptions of those whose knowledge is limited to a few hard technical terms. With us, the Gentlemen of the Faculty have made less progress than those of law and divinity: the latter, indeed, have much to do before they can attain real eminence.

In your profession I have long considered it a desideratum to have an able but simple work, accurately describing the nature and functions of the several parts of man in a state of health, the effect or changes diseases produce on each of those parts and of the remedies for those diseases.

I would purchase and read such a work with pleasure, and that pleasure would be enhanced if it was simple, plain and free, so far as the nature of the subject would admit, from abstruse technical terms, and of attachment to existing theories. Mystery is the enemy of improvement, and it is better suited to prolong the reign of ignorance and of error than to promote that of truth and science. And, the knowledge of things is vastly more important than that of words.

I really wish we had an accurate Journal kept in different sections of our Country of the actual state of the weather, the crops, the general diet and regimen of our citizens, the diseases most prevalent in each, their type, character and mode of treatment, etc., so as to exhibit the means by which health was preserved and lost and how far they depended on climate and modes of living.

Such a Society, I think, might be formed of Gentlemen living in various parts of our Country, with little expense and from whose reports much information could be obtained which would be useful to all, and particularly to Medical Characters. I would freely contribute to such an establishment.

But, I am wandering from the object of this letter, which was to thank you for your Pamphlets and to say, that if you or the Historical Society of N. Y., should need any of the few pamphlets we publish here, it will afford me pleasure to procure and transmit them. I remain with much esteem and respect, Yours, etc., William Plumer.

About 1817 Spalding began to agitate the preparation of a national pharmacopœia, notwithstanding the fact that several local pharmacopœias already existed, the most extensive and authoritative one being that of Massachusetts. His motive in urging a national pharmacopœia was due to his desire to secure uniformity, and also to discard local remedies which seem to have been used in different parts of the United States without any sufficient scientific authority. As an example of such local favorites may be mentioned scutellaria or skullcap as a remedy for hydrophobia. It was shown by Spalding that the authority for the use of this remedy was wellnigh universal. Numerous cures through its employment were reported, and in the literature its claims were overwhelming. We now know that it is worthless, and its elimination from the pharmacopœia was promptly made. The plan proposed by Spalding for the preparation of the pharmacopœia was an excellent one, and has practically been followed for the last 100 years.

The pharmacopœia was originated in a paper by Dr. Spalding, read before the medical society in the city of New York, in which he pointed out the difficulties attendant upon the present lack of uniformity in the preparation of drugs in the different states. As a result of the discussion which followed the reading of his paper, a committee was appointed, of which Dr. Spalding was chairman, to suggest measures for the preparation of a national pharmacopœia. The country was divided into four districts, known as the northern, middle, southern and western. Through the medical societies of these regions, delegates were chosen to meet at some central point in the district to discuss matters pertaining to the drugs to go into the pharmacopœia, and to elect two delegates, each to go to Washington later to prepare the book for publication. The only two district conventions were those of New England, at Boston, and of the Middle States at Philadelphia, which met on June 1, 1819. The meeting in Philadelphia, although attended only by delegates from the middle district, had done valuable work in the discussion of remedies and methods. The delegates chosen at the two district meetings met in a general convention in Washington on January 1, 1820, Dr. Spalding being one of the delegates. The two rough drafts from the district meetings were examined and discussed, and the preparation of the pharmacopœia was outlined and plans made for its completion and adoption. A Committee of Publication was chosen, with Dr. Spalding as chairman, which met in New York in June, 1820. The pharmacopœia was printed in English and Latin, and was immediately adopted as authoritative throughout the country.

About the same time Dr. Spalding also had, in addition to the pharmacopœia, a plan for the establishment of what he termed a medical police to have charge of all sanitary matters. The latter scheme, however, seems to have faded from public sight.

Dr. Spalding did not live long after the publication of the pharmacopœia. In 1821, while walking in the city of New York, he was struck down by some building material which fell upon his head, and rendered him unconscious. Although he recovered apparently, he never enjoyed good health, and gradually went into a state of physical and mental decline. He gave up practice, sent his family to New England, and later rejoined them there. He died on October 21, 1821, a few days after he reached them.

It is evident that he was a man of unusual ability, being industrious, efficient, and with large powers of initiative. Imperfectly educated as he was, he had made himself an excellent physician, a remarkable surgeon and anatomist, an interesting and inspiring medical teacher, and a member of the profession full of enthusiasm for its advancement and perfection. He was denied the great desire of his life, the privilege of studying abroad, and doubtless had he been able to do so, and had returned to America with the new ideas, his subsequent labors might have resulted in great additions to the medical knowledge and resources of the country. The story of his life is a most inspiring one.

NOTE.—Since the above sketch was written and presented to the Historical Club, Dr. Kelly has placed in my hands a copy of the first edition of the Pharmacopœia of the United States of America. It bears the following title page:

The
PHARMACOPOEIA
of the
UNITED STATES OF AMERICA.
1820.

By the
Authority of the Medical Societies and Colleges.

BOSTON

Printed by Wells and Lilly.
For Charles Ewer, No. 51, Cornhill.

Dec. 1820.

It is bound in leather and is in excellent state of preservation. The name on the fly leaf cannot be deciphered definitely. It is in pencil and is dim in places. The inscription seems to be James Burbeck, 1827. It has undoubtedly belonged to a druggist or apothecary as it contains many recipes neatly interleaved in various portions of the book. There are also prescriptions for various diseases. The book contains an interesting Historical introduction explaining the object of the preparation of the National Pharmacopœia. There is also a Preface which gives full details as to the movements which led up to the preparation of the work. In the list of delegates originally selected to attend district conventions to prepare lists of medicines and to select local committees are to be found names eminent in the profession one hundred years ago, many of whom figured in medical literature. A good many of them also were members of the final committee which prepared the National Pharmacopœia.

From New York there were: David Hosack, Samuel L. Mitchell, T. Romeyn Beck, Lyman Spalding, John W. Francis and Valentine Mott. From Massachusetts: John C. Warren, Jacob Bigelow, James Thacher and George C. Shattuck. From New Haven: Eli Ives and Nathan Smith. From Philadelphia: T. T. Hewson and Joseph Parrish. From Maryland: Nathaniel Potter, Elisha DeButts, Samuel Baker and Ennals Martin.

THE EFFECT OF DIFFERENT BLOODS ON THE GROWTH OF *B. INFLUENZÆ*¹

By T. M. RIVERS, M. D., Baltimore, Md.

The growth of *B. influenza* has been described as small dew-drop colonies invisible by direct light, but becoming larger when near colonies of other bacteria, as staphylococci, pneumococci and streptococci, this latter phenomenon being called obligate symbiosis. This is a correct description of the colonies as they appear on human blood agar.

In making routine throat cultures it was noticed that on certain days the colonies of *B. influenza* were large and easy to isolate, whereas on other days they were very small and often overlooked. The results from day to day differed so much that an explanation was sought. It was found that on the days when the colonies were large either cat or rabbit blood had been used and human blood when they were small or over-

looked. This led to the comparison of the effects of different bloods and sera on the growth of *B. influenza*.

In three petri dishes respectively was placed 0.5 c. c. human, 0.5 c. c. cat and 0.5 c. c. rabbit blood. Then 10 c. c. of meat infusion agar were added at 40° C. from the same flask to each of the dishes. After the agar had solidified, each plate was streaked with a broth suspension of two strains of *B. influenza*. The growth on the rabbit blood (Fig. 1) and cat blood agar was luxuriant. The colonies which were well separated became very large and slightly opaque, and when they were 48 hours old some were umbilicated or checker-shaped. The growth on the human blood agar (Fig. 2) appeared very slowly and at the end of 48 hours was still seen with difficulty.

Three other plates were made as above and streaked with a broth suspension of *B. influenza*. In the center of each plate there was the streaked fluid containing the

¹From the Departments of Pediatrics and Pathology, Johns Hopkins University.

cocci. On the rabbit blood and the cat blood agar the colonies of *B. influenza* grew best at the edges where they were well separated. There was no tendency to be largest near colonies of pneumococci (Fig. 3). On the human blood agar the colonies of *B. influenza* were just visible at the edges but grew large near pneumococcus colonies (Fig. 4). This has been repeated with six lots of meat infusion agar and each time the difference has been observed.

B. influenza grows well on rabbit blood agar, cat blood agar and Avery medium when 1 per cent of washed cells is added to the agar at 95° C. There is also no difficulty in growing the bacillus on "chocolate blood agar" even when human blood is used. If the "chocolate agar" is good there is no obligate symbiosis, but at times, when the medium is improperly made, this occurs. Very rarely does the symbiotic relationship appear on rabbit or cat blood agar.

It would seem that fresh human blood either has an inhibitory effect on the growth of *B. influenza* which pneumococci or other bacteria remove by their growth, or else it lacks something which is supplied in the neighborhood of other bacteria by the products of their metabolism. The fact that it grows well on Avery medium and on "chocolate human blood agar" makes it seem most likely that there is an inhibitory factor which is removed by heating or by the growth of other bacteria.

Two tubes each containing 0.5 c. c. of defibrinated human blood were inoculated respectively with approximately 100,000 influenza bacilli and pneumococci. Two tubes of 0.5 c. c. defibrinated rabbit blood were likewise inoculated. A loopful from each was streaked on a separate rabbit blood agar plate 20 minutes later. There was a heavy growth (400-500 colonies) on all the plates except the one streaked from human blood and influenza bacilli which had only several colonies. After four hours' incubation a good growth was obtained from all except human blood and influenza bacilli which was sterile. To be certain it was sterile an extra plate was streaked with one-tenth of the contents of the tube. Still no growth was obtained. This precaution was taken because it had been observed that influenza bacilli occur in chains and clumps in human blood and serum whereas in smears from rabbit blood and serum they are found diffusely scattered. Clumping could account for a marked difference in the number of colonies from a loopful, but not for a sterile plate from one-tenth the contents of a tube.²

Approximately 100,000 influenza bacilli were added to 0.5 c. c. meat infusion broth, 0.5 c. c. normal human serum, and 0.5 c. c. rabbit serum. The broth was used as a control. The tubes were incubated for two hours and a loopful from each was streaked on a blood agar plate. A heavy growth was obtained from the broth, less from the rabbit serum, and only a few colonies from the human serum. After 18 hours' incubation, the human serum was sterile while there was a heavy growth from the rabbit serum (Figs. 5, 6, 7, 8, 9).

² Uniformity of growth has been sought by using rabbit blood agar for plating and for each experiment the plates were all poured at the same time from one large flask of meat infusion agar.

Sera from four adults and one infant, some of whom had had influenza, others not, have been tried with several strains of influenza bacilli and all have shown a bactericidal effect. Sterile plates cease to be obtained at different points in the dilutions of the various sera when a constant number of bacilli are used for an inoculation. The same is true when one serum is used and the number of bacilli inoculated is varied. Normal human serum kills influenza bacilli rapidly, in many instances causing the death of thousands of bacteria in 20 minutes at room temperature. This bactericidal property is lost very rapidly upon dilution. Rabbit serum, also, is slightly bactericidal and, if a light inoculation is used, the undiluted normal serum may yield a sterile plate. There is no comparison, however, between the two sera. Guinea-pig serum, too, is not very bactericidal for *B. influenza*.

Inactivating human serum at 54° C. for one-half hour markedly decreases its bactericidal properties for *B. influenza*. Normal rabbit and guinea-pig sera were tested at the same time with normal and inactivated human serum. Rabbit serum decreased the number of colonies at first, but this effect soon disappeared and at the end of 18 hours a heavy growth was obtained from the rabbit and guinea-pig sera. Even inactivated human serum kills in 12 to 18 hours.

EXPERIMENT SHOWING THE DIFFERENCE BETWEEN NORMAL AND INACTIVATED HUMAN SERUM. THE COUNTS ARE REPORTED IN ROUND NUMBERS FOR CONVENIENCE

Dilutions of normal and inactivated human serum		Approximate inoculation of each tube with <i>B. influenza</i>	Number of colonies obtained at different times by streaking a loopful from each tube on a blood agar plate					
			20 minutes		4 hours		18 hours	
Serum	Locke's Solution		Normal	Inactivated	Normal	Inactivated	Normal	Inactivated
1.00 c. c.	0.00 c. c.	100,000	35	300	0	300	0	0
0.75 c. c.	0.25 c. c.	100,000	20	300	0	300	0	10
0.50 c. c.	0.50 c. c.	100,000	40	200	0	300	0	200
0.25 c. c.	0.75 c. c.	100,000	150	250	0	300	0	400

Attempts have been made to reactivate the inactivated human serum with rabbit and guinea-pig serum as they do not inhibit the growth of influenza bacilli to any great extent. This has been accomplished a number of times. It has been accomplished also with normal human serum. An objection might be raised to the use of normal human serum because it is in itself bactericidal. The experiment as shown in the table on page 131 seems to show that it can be done.

During the epidemic of influenza last fall thousands of ante-mortem and post-mortem blood cultures were taken and very few positive results were reported for *B. influenza*, despite the fact that at autopsy they were as numerous in many of the lungs as pneumococci and hemolytic streptococci which were easily obtained in a large percentage of the post-mortem blood cultures. Positive blood cultures are at times obtained from patients with influenza endocarditis and from children with

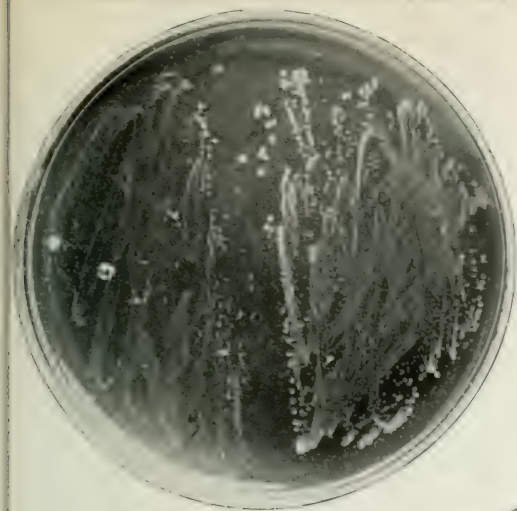


FIG. 1.—Forty-eight hour growth of two strains of *B. anthracis* on 5 per cent rabbit blood meat infusion agar.

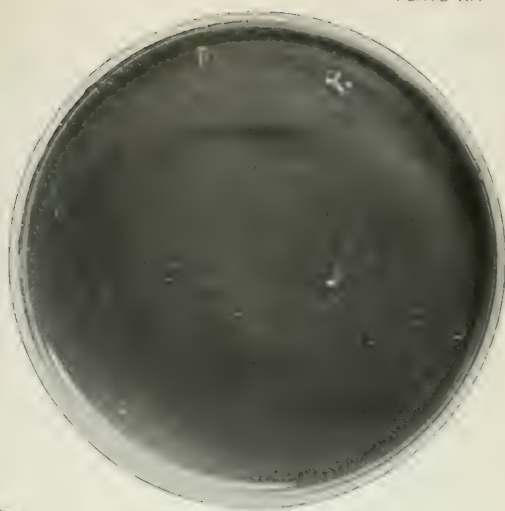


FIG. 2.—Forty-eight hour growth of two strains of *B. anthracis* on 5 per cent human blood meat infusion agar.

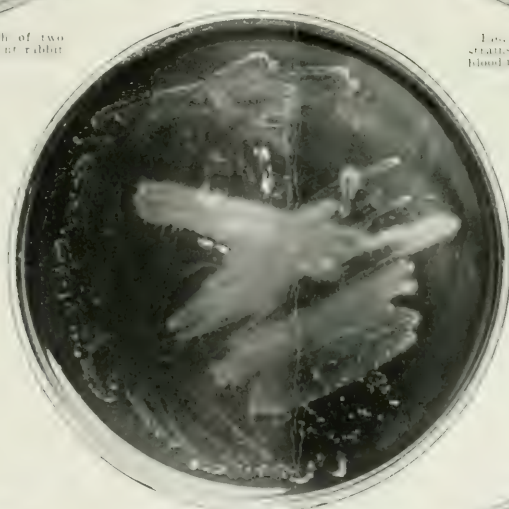


FIG. 3.—Atypical *B. anthracis* on 5 per cent rabbit blood meat infusion agar.

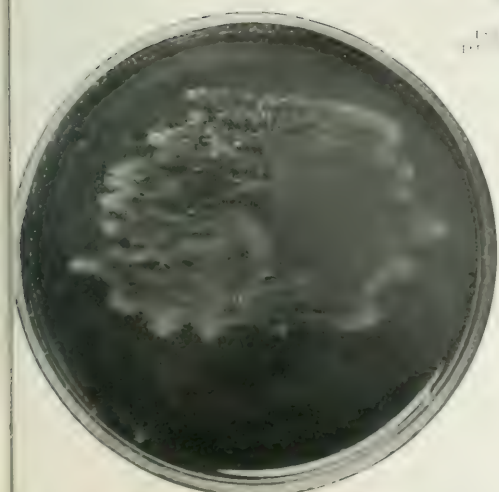


FIG. 4.—*Proteus morganii* on 5 per cent human blood meat infusion agar.



FIG. 5.—*Proteus morganii* on 5 per cent rabbit blood meat infusion agar.



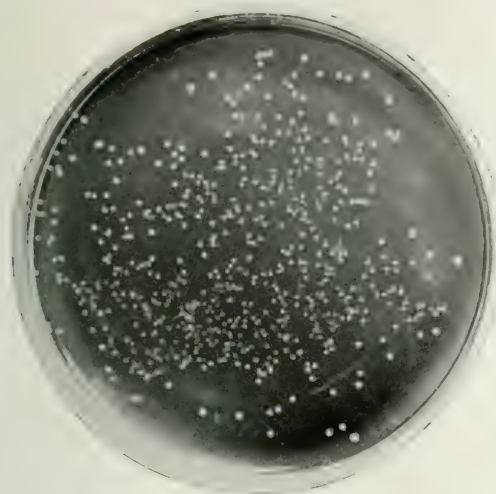


FIG. 6.—Growth obtained as in Fig. 5 except that rabbit serum was used instead of broth.

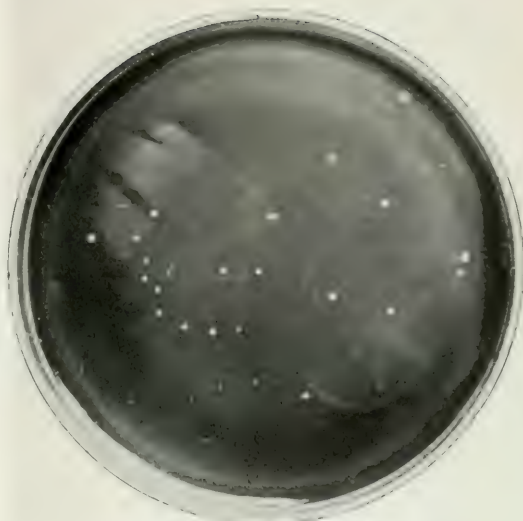


FIG. 7.—Growth obtained as in Fig. 5 except that human serum was used instead of broth.

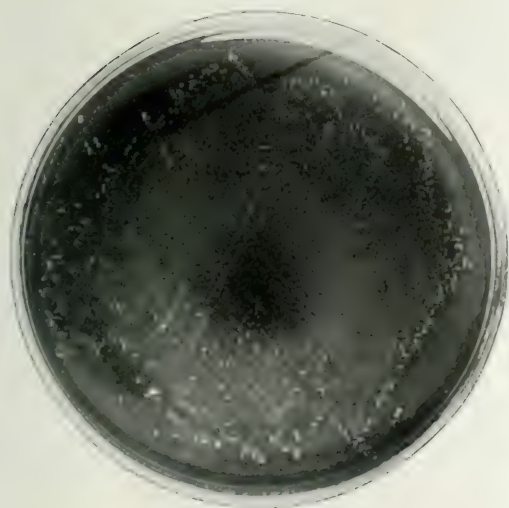
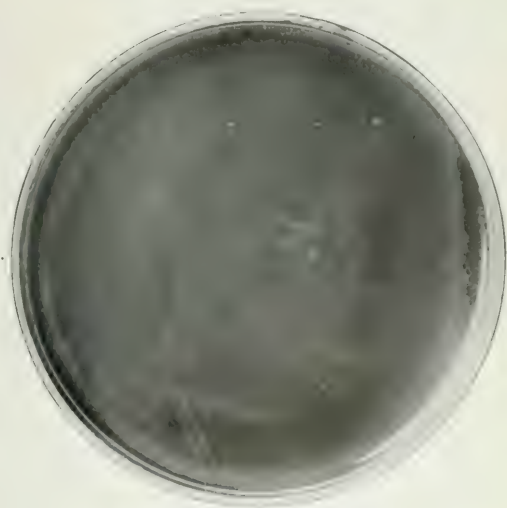


FIG. 8.—Growth obtained as in Fig. 6 except that incubation was for eight hours instead of 24 hrs.





influenza meningitis, but these are the exception when compared with the patients who died during the epidemic and had influenza bacilli in the lungs at autopsy. *B. influenza* either does not invade the blood stream, is promptly killed when it does, or, if alive, is not recovered by the present cultural

EXPERIMENT TO SHOW REACTIVATION OF THE INACTIVATED HUMAN SERUM AND RESTORATION OF ITS BACTERICIDAL PROPERTIES. THE COUNTS ARE REPORTED IN ROUND NUMBERS FOR CONVENIENCE

Types of different sera with dilutions, 1 c. c. in each tube	Approximate inoculation of each tube with <i>B. influenza</i>	Number of colonies obtained in streaking blood agar plates with a loopful from each tube at different times					
		5 min.	1 hr.	2 hrs.	4 hrs.	7 hrs.	24 hrs.
0.5 c. c. normal human serum.	100,000	400	0	0	0	0	0
0.5 c. c. inactivated human serum.	100,000	400	400	400	200	125	0
0.4 c. c. inactivated human serum + 0.1 c. c. normal human serum.	100,000	400	50	25	0	0	0
0.4 c. c. Locke's solution + 0.1 c. c. normal human serum.	100,000	400	300	200	300	400	0

methods. As shown above, human serum and defibrinated blood are very bactericidal for the influenza bacillus *in vitro* as compared with other bloods used and also as compared with the pneumococcus. This bactericidal property is lost rapidly upon dilution, and laboratory strains have been grown in

100 c. c. of meat infusion broth with 10 c. c. human blood added even when very light inoculations have been made (less than 100 bacteria). Although conclusions cannot be drawn concerning happenings *in vivo* by what occurs *in vitro*, may it not be possible that a combination of such factors accounts for so many negative blood cultures for *B. influenza* when they are so abundant in many lungs at autopsy?

CONCLUSIONS

1. *B. influenza* grows well and produces large, often opaque, colonies, upon the proper medium.

2. *B. influenza* grows better on rabbit blood and cat blood agar than on human blood agar. Some of the discrepancies between the findings of various laboratories during the epidemic may be explained possibly by the difference in the media used.

3. Obligate symbiosis occurs more commonly on human blood agar than on rabbit or cat blood agar and in part, at least, is due to the inhibitory effect of the blood which is removed by heating or by the growth of other bacteria.

4. Defibrinated human blood and normal human serum are very bactericidal for the strains of influenza bacilli studied as compared with defibrinated rabbit blood, normal rabbit serum and normal guinea-pig serum.

5. Inactivated human serum, although less bactericidal than normal serum, also kills in from 12 to 24 hours.

6. There is evidence that the marked bactericidal properties can be restored to inactivated human serum by a quantity of normal human serum which by itself is not bactericidal in the same length of time. Reactivation can be accomplished by other normal sera.

OBSERVATIONS ON THE CLINICAL PHARMACOLOGY OF DIGITALIS

By ALFRED M. WEDD, M. D., Pittsburgh, Pa.

(From the Medical Clinic of the Cleveland City Hospital, Service of Dr. E. P. Carter)

Although introduced into therapeutics by Withering in 1785, digitalis received but little consideration from medical scientists until comparatively recent years, and the modern clinical knowledge of the drug may be said to date from the work of Mackenzie,¹ reported in 1911.

The present communication is compiled from data on unselected cardiac and cardiorenal patients admitted to the City Hospital during the past year to whom digitalis was given, including 29 in whose cases electrocardiographic records were taken every 24 hours, or more frequently, during the period of administration of a standardized preparation of the drug.

PREPARATION AND DOSAGE

The preparation was the tincture, two different lots being used, each of which had been standardized by Prof. R. A.

Hatcher, of Cornell University. Digitalis dosage, referring to the tincture, in clinical practice is subject to rather wide variation; from a daily dose of 1 c. c. or less, used by some practitioners, through the dose of from 4 to 6 c. c. recommended by Mackenzie, up to the massive doses of 15 to 25 c. c. in 24 hours (usually 0.146 c. c. per pound of body weight), advocated by Eggleston² and recently studied and endorsed by White and Morris.³

In this work it was desired to give enough of the drug to bring the patient promptly under its influence, but to avoid such amounts as might by the early production of toxic symptoms prevent us from following its progressive action. The daily dose used was from 8 to 12 c. c., usually 10 c. c., and this was continued until definite evidence of digitalis action was

¹ Mackenzie: Heart, 1911, XI, 273.

² Eggleston: Arch. Int. Med., 1915, XVI, 1.

³ White and Morris: Arch. Int. Med., 1918, XXI, 740.

noted. The indications to discontinue the drug were alimentary disturbances, derangements of the cardiac mechanism or slowing of the pulse rate to a level beyond which it was deemed inadvisable to continue.

The cat unit of Tincture A was 1.11 c. c. and it was, according to Professor Hatcher, a fairly good specimen. This preparation was given to five patients. The following are brief details of these cases:

No. 320. Diagnosis, chronic myocarditis. Age, 16 years; body weight, 125 pounds. Total dose, 72 c. c. Rate while in bed slowed to 60.

No. 299. Diagnosis, chronic myocarditis. Age, 44 years; body weight, 140 pounds. Total dose, 115 c. c. No clinical effect.

No. 321. Diagnosis, chronic myocarditis and nephritis. Age, 48 years; body weight, 135 pounds. Total dose, 101 c. c. Rate, when up, reduced from 120 to 110. No toxic symptoms appeared.

No. 323. Diagnosis, chronic myocarditis and nephritis. Age, 52 years; body weight, 140 pounds. Total dose, 137 c. c. Pulse slowed from 120 to 60 after 119 c. c., then increased to 84 and remained at that rate. No toxic symptoms.

No. 332. Diagnosis, chronic myocarditis with atrial fibrillation, nephritis. Age, 45 years; body weight, 140 pounds. Total dose, 149 c. c. Pulse rate slowed to 56. No toxic symptoms.

These were the first cases studied and in three of them the drug was discontinued because it was feared that some unexpected result might occur, since the dosage then far exceeded that usually given.

In the remaining work a second tincture was used, the cat unit of which was 0.85 c. c. The total dosage with this preparation showed considerable individual variation. In No. 368 nausea and vomiting occurred after 20 c. c., while in No. 374, 100 c. c. were given without the development of any toxic symptoms. Because of an oversight No. 304, a case of complete dissociation, received 280 c. c. during a period of 10 weeks without showing any clinical symptoms. In nine cases toxic symptoms were produced by 40 c. c. or less; in seven cases, by 40 to 60 c. c.; six patients took from 95 to 100 c. c. The average total dose required for the production of toxic symptoms in 22 patients was 52 c. c.

No. 321 entered the hospital a second time six months after the first admission, with moderate decompensation, presenting a clinical picture similar to that when first seen. Digitalis was again given and nausea and vomiting occurred after 35 c. c. of the second tincture, whereas 100 c. c. of the first produced no clinical effect. The inefficiency of the first tincture was undoubtedly due to delayed absorption from the alimentary tract, as will be shown when the effect of digitalis on the T-wave is considered, but the cause of this is not known. It is evident, however, that biological standardization showing approximation to theoretical strength is no guarantee of the clinical efficiency of a given preparation of the drug. Individual power of absorption for a given tincture appeared to be quite uniform, so variation in toxic dosage is due to variation in individual tolerance for the drug.

No constant relation between the amount of digitalis that could be given and the age or body weight of the patient or the condition of the myocardium could be discovered.

EFFECT ON EDEMA, DYSPNEA AND CYANOSIS

That digitalis has no specific diuretic effect is now generally recognized. The decrease in edema depends on improvement in the circulation, and rest in bed alone is an important factor in bringing this about. In three purely cardiac cases the edema had almost entirely disappeared before any digitalis action was recorded. Its removal in cardio-renal cases was much more slowly accomplished. The value of determining the output of phenosulphonaphthalein before and after the administration of digitalis may be pointed out as a means of determining the relative cardiac and renal elements in the original clinical picture.

The alleviation of dyspnea was also seen to be an indirect digitalis effect, depending on improved pulmonary circulation, the rest, morphin and venesection, when used, affording the immediate relief, while more permanent removal of this distressing symptom came with improvement in the myocardium.

Cyanosis was a characteristic and persistent sign of myocardial involvement. In those cases in which true myocarditis was believed to be present, and especially in those whose electrocardiograms showed intraventricular or bundle branch block, even though free from edema and dyspnea on moderate exertion, the cyanosis was not influenced by any treatment.

THE EFFECT ON THE HEART RATE

It was formerly maintained that the function and the principal action of digitalis was to slow the pulse. However, excessive slowing with the ordinary use of the drug usually occurs only in atrial fibrillation, and according to Cohn^{*} reduction in rate is not constant, and to produce slowing is not a function of digitalis in therapeutic doses. In five cases of fibrillation the pulse rate was reduced to 55 or lower before or without the onset of toxic symptoms; in one case it fell from 120 to 84 when nausea and vomiting occurred.

Eighteen cases with normal mechanism were studied; in five the rate fell to 60 or lower; in three there was no change; in the remainder the reduction of the initial rate varied between 8 per cent and 33 per cent, the average fall being about 20 per cent. Contrary to the statement of Sollman[†] that fairly normal hearts are slowed by large doses, but that this is due to blocking of impulses from the atrium, the rate in six cases was reduced to 65 or lower before the onset of toxic symptoms with an increase in the P-R interval varying from 0.02 to 0.05 sec. as the only sign of block. In one case the rate after 10 c. c. had increased from 89 to 96 and after 20 c. c. nausea and vomiting occurred, the rate remaining at 96. In a number of cases after reaching a low level the rate increased as the point of toxicity was approached, *e. g.*, No. 323; rate after 119 c. c., 60, after 137 c. c., 84. This is comparable to the experimental findings of Robinson and Wilson[‡] in which slowing continued until about three-fourths of the

^{*}Cohn: *Jour. Amer. Med. Assn.*, 1915, LXIV, 463.

[†]Sollman: *Manual of Pharmacology*, 1917, Philadelphia.

[‡]Robinson and Wilson: *Jour. Pharm. and Exp. Therap.*, 1918, X, 491.

lethal dose had been injected when acceleration set in and continued until fibrillation replaced the normal beat. This acceleration is due, according to Cushny, to increased irritability of the heart muscle rather than to any nerve influence.

It does not seem possible to form any definite conclusion about the time factor in the slowing of the initial rate. Usually there was a gradual fall of from four to ten beats daily. Other agents than digitalis, the rest in bed and the sedatives given, certainly contribute to the first sudden lowering which occurs before there has been time for any specific digitalis action. Thus, in No. 329, a case of fibrillation, an initial rate of 168 fell to 108 in 12 hours, during which 10 c. c. of the tincture had been given. Comparing this with other cases it does not seem reasonable to attribute this prompt reduction of 60 beats solely to digitalis. In general, there seemed to be a gradual decline in rate, which in the fibrillation cases nearly always progressed to a much lower level.

In each of 13 cases of atrial fibrillation examined while under the influence of digitalis, an increase in rate occurred following the administration of atropin (the dose usually given was 2 mgr.). In all of these cases in which the effect of atropin was studied both before and after digitalis, the maximum rate after atropin in the digitalized heart was not equal to that obtained before any digitalis was given; in five of six cases this decrease was exactly 60 beats, and in one 72 beats. Atropin was given to 13 cases with normal mechanism before and after the course of digitalis; in seven there was a decrease in the maximum escape ranging from 4 to 32 beats; in three there was an increase in the maximum of 3, 4 and 17 beats, respectively; three cases showed no escape after digitalis.

THE EFFECT ON THE BLOOD PRESSURE

Although the digitalis bodies produce a characteristic rise of blood pressure in animals, the effect on the pressure in man is very variable. The subject has been recently reviewed and studied by Eggleston.⁷ In 16 cases the blood pressure was carefully followed; in 10 there was no appreciable change; in three the systolic increased without change in the diastolic; in two cases with high pressure the systolic fell 35 mm. and 30 mm., respectively, with a corresponding reduction in the diastolic of 10 mm. and 25 mm.; in one the diastolic fell 25 mm. while the systolic remained unchanged. The conclusion is that the alteration in blood pressure is again an indirect digitalis effect which depends on the improvement in the circulation and is always in the direction of the optimum pressure for the individual.

TOXIC EFFECTS

The manifestations regarded as evidences of digitalis toxicity were all included in the alimentary disturbances or cardiac irregularities. From 24 to 36 hours before actual nausea and vomiting occurred, many patients complained of general malaise, often headache or of some indefinite and indescribable sensation of discomfort and usually refused food.

Considering 20 cases, nausea occurred in 12 and vomiting in six of these; diarrhoea was encountered five times. In nearly all cases these disturbances disappeared promptly after discontinuance of the drug. In No. 355 nausea and diarrhoea persisted for four days. This was the only instance of anything that might be regarded as evidence of the so-called cumulative action of digitalis. The central origin of the nausea and vomiting produced by digitalis has been established by the work of Hatcher and Eggleston.⁸ In six cases it was necessary to discontinue the digitalis because of the onset of serious cardiac irregularities unaccompanied by alimentary symptoms.

DIGITALIS IRREGULARITIES

Digitalis "coupling," a familiar sign of excessive digitalis dosage, appeared twice in the series. The occurrence of premature beats at irregular intervals was frequently seen, usually at the time of other evidences of toxicity. These premature beats, an expression of heightened irritability of the ventricular muscle, always disappeared after atropin.

Sinus arrhythmia due to digitalis occurred in two cases. In No. 334 (see Fig. 1D) it disappeared promptly after atropin, but returned and persisted, though gradually decreasing, for 10 days. In No. 375 the arrhythmia was not removed by atropin, although there was an escape of the pacemaker (Fig. 5D).

Production of "pulsus alternans," described by Mallet and others was not encountered. In one case in which that condition was originally present the alternation disappeared under digitalis (Fig. 2). Similar results have been reported by Windle.⁹

In No. 342 after 25 c. c. of digitalis atrial tachycardia with irregular ventricular response and varying conduction time was present. Normal mechanism was restored by atropin (Fig. 3).

That complete atrioventricular dissociation may occur during the administration of digitalis is well known. Christian¹⁰ has reviewed some of the literature and reported cases. Robinson and Wilson¹¹ have shown that in cats with the vagi intact complete dissociation constantly occurs when 75 per cent of the minimum lethal dose has been given; with the vagi cut, the effect on conduction is not constant. In two cases transient complete dissociation occurred, beside the case of atrial tachycardia with high-grade block previously mentioned. The production of dissociation by action on the inhibitory mechanism is illustrated in Fig. 4, which shows in sequence, prolongation of the P-R interval, dropped beats and dissociation. In these cases of dissociation atropin restored the normal mechanism and this persisted during the hour under examination in the laboratory and was still present at examination 12 hours later. That "escape" from vagus action on the conduction system may occur is illustrated in Fig. 5; the P-R interval had

Hatcher and Eggleston. *Jour. Pharm. and Exp. Therap.*, 1912, IV, 113.

⁷Windle: *Quart. Jour. Med.*, 1917, X, 274.

¹⁰Christian: *Arch. Int. Med.*, 1915, XVI, 341.

⁸Eggleston. *Jour. Amer. Med. Assn.*, 1917, LXIX, 361.

lengthened from 0.12 to 0.22 sec., dropped beats were present and complete block was anticipated; however, a record taken eight hours later showed the mechanism to be normal and the P-R interval 0.16 sec.

CHANGES IN THE ELECTROCARDIOGRAM

Modification of the T-wave of the electrocardiogram by digitalis has been carefully studied by Cohn and his co-workers.¹¹ The following changes in the T-wave were observed in this study: Any degree of flattening of an upright or inverted wave until the isoelectric line was reached; inversion of an upright wave; reversion of an inverted wave; the formation of a diphasic wave, either alone or in conjunction with any other change. The change in the wave continues throughout the administration of the drug so that its conformation varies from day to day with the amount given. Compare the T-waves in Figs. 1 and 3. These changes are attributed by Cohn to an alteration in the muscle balance, resulting in turn in an alteration of the relation of apex to base negativity. This action is for the most part on the myocardium itself. That the true digitalis effect may be masked by vagus stimulation is seen in the changes that frequently occur after atropin. The height or depth of a wave may be affected or reversal may occur, as in Fig. 3. These changes disappear with the action of atropin and the specific digitalis effect is again evident.

In every case the first definite digitalis effect was a change in the T-wave. This was found by Cohn in his cases and Robinson and Wilson⁶ in their experimental study observed the first change to be a flattening or inversion of T, which occurred with 25 per cent of the lethal dose.

A comparison of the T-wave changes produced by each of the tinctures used is interesting and points clearly to slow absorption of the first as the cause of its inefficiency. In No. 320 lowering of T₂ was observed after 16 c. c., definite inversion after 24 c. c. In the four remaining cases in which the first tincture was used an average of 34 c. c. was given before any definite change could be recognized. With the second tincture definite changes were recorded in most cases after 10 c. c. or less. In No. 371 T₁ was lower after 5 c. c.; in No. 368 T₁ was definitely inverted after 10 c. c. Records were seldom taken between 10 and 20 c. c. and no attempt was made to establish the minimum amount that would produce a change.

From this small series in which large doses were used so that changes in more than one wave were recorded simultaneously it is not possible to say which T usually changed first, but it did appear that T₂ is most frequently affected and undergoes the greatest change.

The disappearance of the digitalis action may likewise be followed by changes in the T-wave which begin soon after the drug has been discontinued. The duration of the digitalis effect, as might be estimated by these changes, was not determined.

The alteration in the P-wave seen in some of these cases has been considered elsewhere.¹² In nine cases, 30 per cent of

the series, the P-wave was affected; in eight of these the change occurred only in the third lead, and in one in both the second and third leads (Figs. 1 and 5). In five cases an originally inverted P was rendered upright by digitalis and in three of these the return to the original form was followed after the drug was discontinued. In four of the cases of this group a temporary reversion occurred after atropin. In four cases an originally upright wave was inverted by digitalis and in three of these the wave was reversed by atropin and remained upright, whereas in the fourth the inverted wave was upright 12 hours after the discontinuance of digitalis. Satisfactory explanations for these observations are wanting. There may be a rearrangement of atrial muscle fibers, but the response to atropin in both groups indicates greater vagus influence than in the case of the T-wave. Concerning the limiting of the effect to the third lead, it may be noted that this lead represents primarily the left side of the heart, and all but two of these cases clinically showed marked enlargement to the left, and in six the electrocardiogram was of the type characteristic of left ventricular preponderance.

The occurrence of the U-wave as a component of the ventricular complex in the normal electrocardiogram is recognized. According to Lewis,¹³ it is not uncommon and is related to the early events of diastole. In the records of this laboratory it has seldom been seen. In one case (Fig. 6) a U summit appeared after 30 c. c. of digitalis had been given and continued throughout the remaining observations. It was not due to the appearance of a latent wave with a slower rate, for the rate when it was first seen was faster than the original, and it did not seem to be influenced by atropin. As the patient left the hospital, changes occurring after digitalis was discontinued could not be followed.

In his text Sollman states that, in man, a-v conduction is constantly impaired and that this is an early and positive sign of digitalis action, and Cohn and Fraser¹⁴ found changes in 12 patients studied by them, including four who had no heart lesion. According to White and Sattler¹⁵ "this impairment of conduction is practically entirely due to increased vagus tone" and they report that in every instance after digitalis in which delay in conduction amounted to more than 0.05 sec. atropin reduced the P-R interval to less than its original value. In six of 21 cases in this series there was no appreciable change in the P-R interval. Measurements were made with calipers and a hand lens, but are believed to be sufficiently accurate for clinical purposes. In not one of five cases in which the conduction time was prolonged 0.05 sec. or more did atropin restore the original, and in two cases in which complete dissociation occurred the P-R interval in the normal mechanism after atropin was longer than in the original (Fig. 4). In the case with atrial tachycardia and high-grade block the P-R interval after atropin was the same as the original.

¹³ Lewis: Clinical Electrocardiography, 1913, London.

¹⁴ Cohn and Fraser: Jour. Pharm. and Exp. Therap., 1913-14, V, 512.

¹⁵ White and Sattler: Jour. Exp. Med., 1916, XXIII, 613.

¹¹ Cohn, Fraser and Jamison: Jour. Exp. Med., 1915, XXI, 593.

¹² Carter and Wedd: Arch. Int. Med., 1919, XXIII, 1.

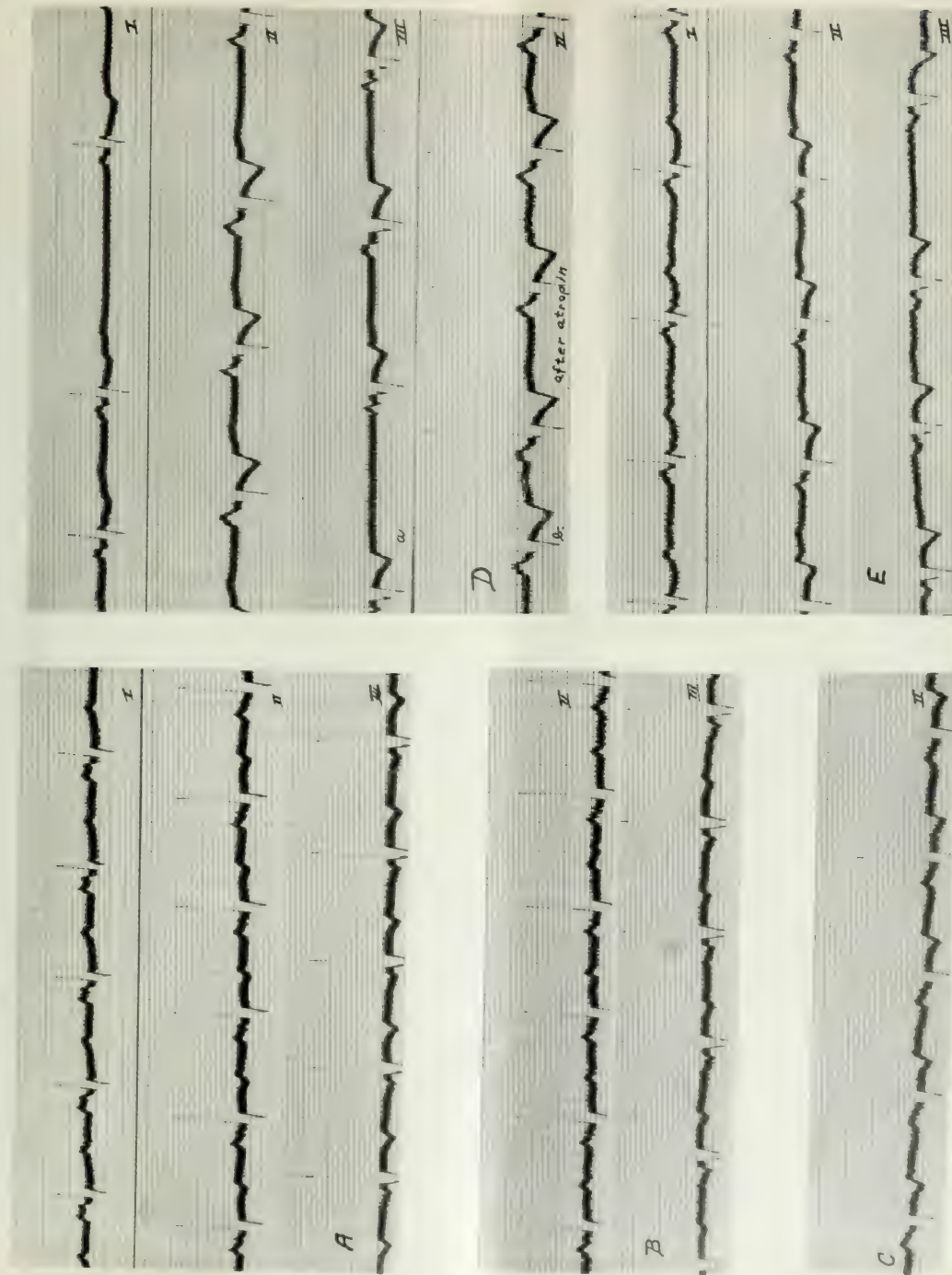


FIG. 1. Case 134. A, on admission; B, after 14 c c. therapy of digitalis; C, after 20 c c.; D, after 25 c c.; E, ten days later.

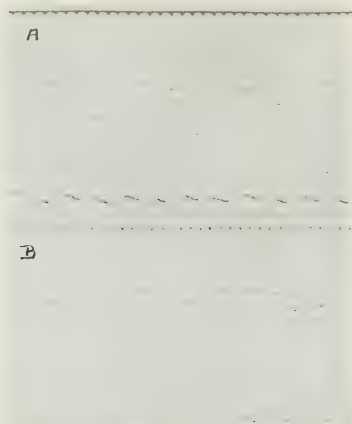


FIG. 2 (Case 321).—A, on admission; B, after 102 c. c. of digitalis.

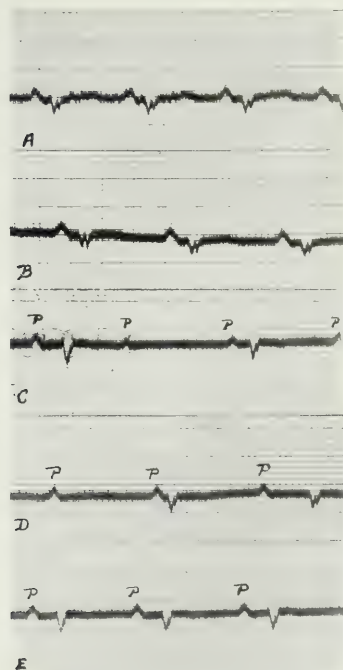


FIG. 4 (Case 351). Lead II.—A, on admission; B, after 24 c. c. of digitalis; C, after 72 c. c.; D, after 96 c. c.; E, after atropin.

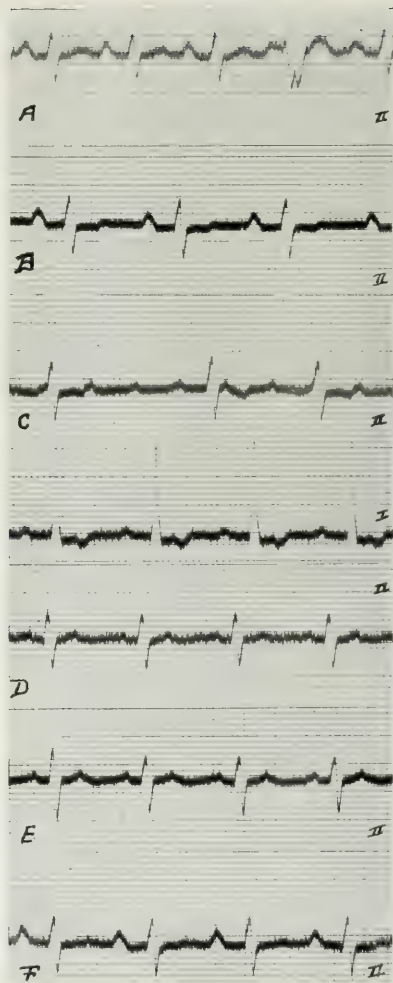


FIG. 3 (Case 342).—A, on admission; B, after 12 c. c. of digitalis; C, after 25 c. c., atrial rate 216, ventricular rate 80; D, 30 min. after atropin; E, 1 hr. after atropin; F, 12 hrs. later.

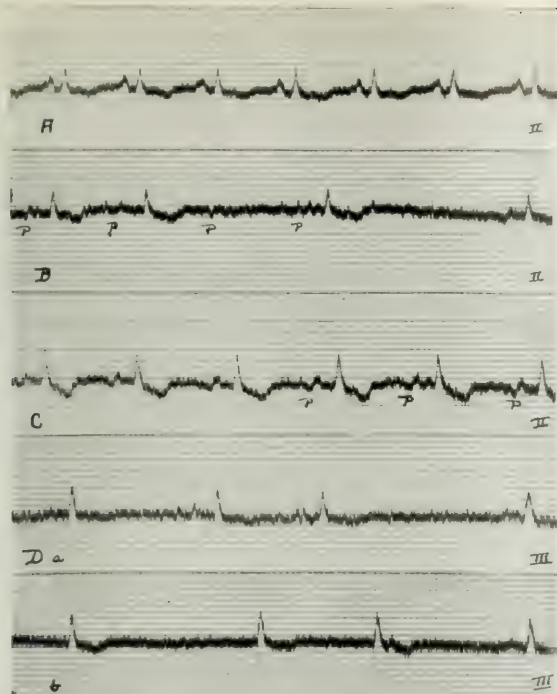


FIG. 5 (Case 375).—A, on admission; B, after 60 c. c. of digitalis, 8 hrs. later; C, after 100 c. c. (a); after atropin (b).

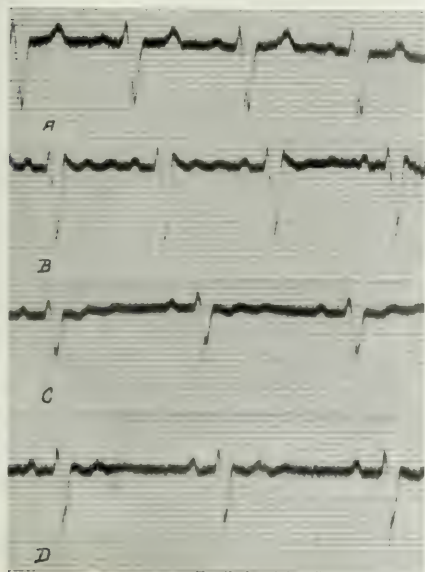


FIG. 6 (Case 374). Lead III.—A, on admission; B, after 30 c. c. of digitalis; C, after 90 c. c.; D, after atropin.



FIG. 7 (Case 354). Lead II.—A, on admission; B, after 22 c. c. of digitalis; C, 19 hrs. later, after 29 c. c. (a); after atropin (b). D, after 29 c. c. (a); after atropin (b).

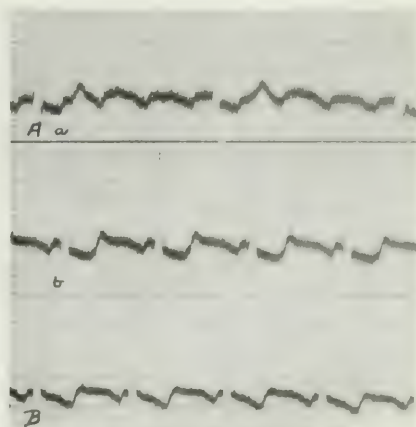


FIG. 8 (Case 297). Lead II.—A, on admission; B, after 30 c. c. of digitalis, 3 hrs. later; C, after atropin (b); B, 30 c. c. later.



Direct action on the conducting tissue may be illustrated by No. 323: original P-R, 0.120; after digitalis, 0.213; after atropin, 0.163, and there was no escape of the pacemaker. In No. 279 in which a lengthening of 0.02 sec. occurred there was no shortening of conduction and no sinus escape after atropin. Also consider the P-R intervals in Fig. 7. In other cases there was partial or complete reduction of the conduction time. The data obtained tend to show that impairment of conduction by digitalis may be due to either increased vagus tone or to direct action on the conducting system, or to a combination of both, which is the usual mechanism in cases of pronounced action.

Definite impairment of conduction was certainly not an early evidence of digitalis action, but a gradually progressive one, and an appreciable change in its time relation seemed comparable to the finding of Robinson and Wilson, that prolongation of conduction time occurred after 50 per cent of the lethal dose had been given.

But few cases with an original conduction time of more than 0.18 sec. were studied. In No. 364, a referred patient, an original conduction time of 0.25 which had been increased to 0.29 by 12 c. c. of digitalis was restored completely by atropin. The possibility of escape from digitalis action on the conduction system has been mentioned (Fig. 5). No criterion was apparent by which a marked effect on conduction might be predicted and the conclusion reached is that of Cohn,⁴ that any effect on conduction is a specific effect of the drug, apart from any pre-existing damage in the system.

ACTION IN FIBRILLATION AND FLUTTER

There is sufficient satisfactory experimental evidence that digitalis produces its characteristic effects by acting centrally in the medulla and locally on the heart muscle. The usual test for differentiating central and local action is the behavior after removal of vagus influence, by section of the nerve or the use of atropin. That the various digitalis effects may be produced in man through either mechanism alone or through both simultaneously has been pointed out when considering the specific digitalis actions.

In 1871 Traube showed that digitalis slowing was due to stimulation of the vagus center and this has been confirmed by many experimenters since that time. Cushny¹⁰ has demonstrated that in the perfused mammalian heart, in certain rare cases with normal mechanism in man and specially in atrial fibrillation in man, digitalis may slow the pulse independently of the inhibitory mechanism. Robinson and Draper¹¹ have shown in atrial fibrillation in man that mechanical stimulation of the right vagus nerve usually caused marked slowing or stoppage of the ventricular rhythm and state that the ventricular pauses were apparently due to blocking of stimuli from the atria. Hirshfelder¹² found that in dogs with artificially induced fibrillation the heart could be markedly slowed

by digitalis and that the rapid arrhythmia promptly returned after paralysis of the vagi with atropin, and also that further slowing and complete block could be produced after the vagi had been paralyzed, although the fibrillation continued. Commenting on this work, Cushny says: "But this is not the characteristic reaction in clinical fibrillation as he seems to suppose; the slowing in these cases is independent of the inhibitory mechanism."

In all cases of fibrillation under the influence of digitalis to which atropin was given an increase in ventricular rate occurred. Similar results have been reported by Cushny¹⁰ and by Mackenzie. The atria are seen to continue in fibrillation, so there is no functioning pacemaker. Hence the increased ventricular rate must result from an increase in the number of impulses permitted to pass through the conducting tissues, and such an increase brought about by atropin implies a former depression of conduction by vagus tone. That digitalis produces more marked slowing by the direct action on the muscle of the fibrillating heart no one would attempt to deny, but that the vagus center in the medulla, the usual site of action of the drug, should be ignored because of an altered condition of the myocardium which is less obvious. That the decrease in the maximum rate under atropin of the digitalized heart which was observed in 100 per cent of the fibrillating hearts and in 76 per cent of those with normal mechanism may be taken as a measure of the local action of the drug is seemingly a possible interpretation.

From a comparison of the reaction of the perfused heart to digitalis with that of clinical fibrillation, Cushny concludes that the reaction so characteristic of fibrillation is due not to the fibrillation itself but to a more fundamental factor, malnutrition. Furthermore, it is conceivable that because of the faulty circulation of the fibrillating heart an accumulation of cellular metabolites may result, by virtue of an increased H-ion concentration in the production of a more highly glucosidolytic medium, and that because of increased destruction, there may result an increased capacity for digitalis bodies. Similar action may possibly occur in other tissues also and may constitute the mechanism by which many individuals with severe myocardial lesions can take large amounts of digitalis before toxic symptoms appear.

The action of digitalis in atrial flutter, a condition similar to fibrillation, is both central and local (Figs. 7 and 8). In four cases of flutter examined the administration of atropin reduced the block to 2:1. Unfortunately atropin was not given after the change to fibrillation, but in No. 354 the normal mechanism present after the last flutter record shows sinus escape and partial reduction of the conduction time.

SUMMARY

Careful observations on the action of tincture of digitalis have been made in many patients. It was soon apparent that successive tinctures supplied to the hospital wards showed marked variation in their efficiency. Two biologically stand-

¹⁰ Cushny: Jour. Pharm. and Exp. Therap., 1918, XI, 103.

¹¹ Robinson and Draper: Jour. Exp. Med., 1911, XIV, 217.

¹² Hirshfelder: Jour. Pharm. and Exp. Therap., 1915, VI, 597.

¹³ Cushny, Marris and Silberg: Heart, 1912, IV, 33.

ardized tinctures of approximately theoretical strength were studied and it appeared that the inefficiency of one was due to failure of prompt absorption from the alimentary canal, as was indicated by the larger amount necessary to produce a change in the T-wave, the earliest demonstrable digitalis effect.

Daily doses averaging 10 c. c. were given and continued until alimentary disturbances or abnormalities in the cardiac mechanism appeared. In no case was there any ill effect attributable to digitalis and there were no evidences of the so-called cumulative action. The toxic dosage showed marked individual variation, from 20 c. c. to 100 c. c. The earliest signs of toxicity were slight nausea and premature beats. It is believed to be a perfectly safe procedure and one which will promptly bring about the expected benefits of digitalis to begin with an initial dose of 5 c. c. of tincture and to continue with 8 or 10 c. c. daily until signs of toxicity appear or until clinical improvement warrants discontinuing the drug.

The various changes in the electrocardiogram have been considered. Of these alteration in the T-wave was the earliest and most constant. Modifications of the P-wave in the third lead in about one-third of the cases is noteworthy. In one case digitalis appeared to be responsible for the appearance of a

U summit. Definite prolongation of the P-R interval, indicating increased conduction time, was seen in 80 per cent of the cases. In two cases complete dissociation occurred and in one atrial tachycardia with high-grade block, and in all these normal mechanism was promptly restored by atropin.

From a consideration of the effect of atropin on the pacemaker, the ventricular response and the conduction time, it is believed that in all cases the action of digitalis is both central, in the medulla, and local, in the myocardium, with relatively greater local action in atrial fibrillation. Exception is taken to the statement of Cushny that in fibrillation there is no digitalis action through the inhibitory mechanism, and it is suggested that the decrease of maximum rate after atropin of the digitalized heart may be taken as a measure of the local action of digitalis on the myocardium.

In the series studied were cases with all possible valvular defects, all grades of decompensation, renal lesions of varying degrees of severity, systolic blood pressures ranging from 90 mm. to 230 mm. and almost all of the recognized types of myocardial involvement, including cases of intraventricular block, bundle branch block and complete dissociation, and there was not found any clinical entity which might be said to constitute a contraindication to the use of digitalis.

NOTES ON NEW BOOKS

The Principles of Acidosis and Clinical Methods for Its Study.
By ANDREW WATSON SELLARDS, Associate in Harvard Medical School. (Harvard University Press, 1917.)

This work of some 111 pages exclusive of the bibliography deals with acidosis with a terseness of style and elimination of unnecessary detail which make it very interesting as well as valuable to the physician and student. There is careful consideration of the various theories concerning acidosis and the evidence in favor of each is thoroughly discussed.

The first three chapters are given to the consideration of the chemistry of acids and bases, their metabolism in the human body, and methods of diagnosing pathological alterations in the mechanism. Particular attention is paid to the exact importance of change in the alkalinity of the blood and the physiology of the kidney in adjusting its excretion to these changes. In the next chapter the reaction of the body to sodium bicarbonate in health and disease is taken up. The value of observing this reaction is brought out. In this chapter also a very valuable test for the changes in the alkalinity of the blood is described in full.

Succeeding sections deal with the occurrence of acidosis and a definition of the condition. The determination of a definition is most timely, since there is considerable variance among writers as to the exact meaning of the term "acidosis." The part dealing with therapy is very suggestive, although no definite working guide is given. Nevertheless, from a discussion of cases and results sufficient data are given to enable the practitioner to make immediate use of the method described by the author.

By no means the least important part of the work is that contained in the appendix, in which necessary laboratory methods are described fully and clearly. Definite instructions for carrying out the author's test for acidosis are given explicitly. There is also a very helpful method described for determining the patient's tolerance for sodium bicarbonate.

A very important feature of the book is the discussion of the pathological processes in the acidosis of diabetes, nephritis, and Asiatic cholera, with a differentiation of the steps in each. It is perhaps to be regretted that the writer did not take up the more intricate problems of protein, carbohydrate, and fat metabolism with the relation of each to acidosis, or that other acetoneurias were not considered in the same thorough manner. But what the book may lack in this respect it gains in being concise, containing no confusing details, and being available for any one with a rudimentary knowledge of biochemistry and physiology. It is an important contribution both from the standpoint of information contained and also from the suggestions made concerning other problems in the same field which offer rich opportunity for study.

H. M. W.

Trench Fever: Report of Commission Medical Research Committee, American Red Cross. Prepared for publication by RICHARD P. STRONG. (Printed for the American Red Cross Society at the Oxford University Press by Frederick Hall, Printer to the University, 1918.)

Members of Commission: Richard P. Strong, Major, M. R. C., Assistant Director Division Laboratories and Infectious Diseases. In charge Subdivision Infectious Diseases, A. E. F. Homer F. Swift, Major, M. R. C., Senior Medical Officer, No. 1 United States Army General Hospital, B. E. F. Eugene L. Opie, Major, M. R. C., Pathologist, United States Army Base Hospital No. 21, B. E. F. Ward J. Macneal, Captain, M. R. C., Head Department Bacteriology, Central Medical Department Laboratory, A. E. F. Walter Baetjer, Captain, M. R. C., in charge Clinical Laboratory, United States Army Base Hospital No. 18, A. E. F. A. M. Pappenheimer, Captain, M. R. C., Pathologist, No. 1. United States Army General Hospital, B. E. F. A. D. Peacock, Captain, R. A. M. C. (T.), 2d London Sanitary Co. (Entomologist). (Subsequently attached.)

David Rapport, first Lieutenant, M. C., National Guard, A. E. F.

Major Richard P. Strong, M. R. C., in his report on trench fever, has given another proof of the brilliant work which the public is now learning to expect from the army medical corps; and the investigations he reports in regard to trench fever should rank with their model, the classic studies of Reed and his colleagues on the method of transmission of yellow fever. The fact that during 1916 and 1917 no other infectious disease caused so much sickness among the soldiers in France as did trench fever, and its great prevalence at Salonica, in Italy and in Mesopotamia, made it of primary importance. To ascertain the method of its transmission would enable the authorities to take proper preventive measures, and thus much could be done to minimize an enormous wastage among the fighting forces.

Accordingly, Dr. Strong, in October, 1917, was selected by the Medical Research Committee of the American Red Cross to take charge of the work of a special Trench Fever Committee. From that time the committee conferred with the British Army and medical authorities, who were also studying the problem, with the result that in February, 1918, experiments on a group of 82 selected volunteers from the United States Army were commenced. The work was carried on at a stationary hospital of the British Expeditionary Force in France, sufficiently near to the front line to insure the study of trench fever cases early in their course. As the spring offensive was expected in two months' time, the workers had only this short period to investigate the problem before them. There resulted a marvel of coordinated research, which required simultaneous experimentation along many closely associated lines, each modifying the others as the work proceeded. The clinical, bacteriological, serological, louse investigation, blood inoculation and other studies all contributed their part in completing the work, which was reported as it developed to the British Army medical officers, who were also at work on trench fever.

In all a total of 103 different human experiments were carried on in the study of trench fever and its cause, and in these the disease itself was produced experimentally 62 times in different ways. Too much cannot be said in praise of the soldiers of the United States Army who offered themselves so heroically in order to make possible this splendid medical study. The results of this masterly piece of work are best summarized in Dr. Strong's own words:

"The most important facts which have been demonstrated by our investigations are:

"1. That trench fever is a specific, infectious disease; that it is not a modified form of typhoid or paratyphoid fever, and is not related, from an etiological standpoint, to these diseases.

"2. That the organism causing the disease is a resistant, filterable virus.

"3. That the virus causing trench fever is present particularly in the plasma of the blood of trench fever cases, and that such plasma will produce the disease on inoculation into healthy individuals.

"4. That the disease is transmitted naturally by the louse *Pediculus humanus*, Linn., var. *corporis*, and that this is the important and common means of transmission. That the louse may transmit the disease by its bite alone, the usual manner of infection, or the disease may be produced artificially by scarifying the skin and rubbing in a small amount of the infected louse excrement.

"5. That a man may be entirely free from lice at the time he develops trench fever, the louse that infected him having left him some time previously as his host, and that the louse need only remain upon the individual for a short period of time in order to infect him.

"6. That the virus of trench fever is also sometimes present in the urine of trench fever cases, and occasionally in the sputum,

and that the disease may be produced in man by the introduction of the virus in the urine or sputum through the scarified or otherwise abraded skin.

"7. That since the urine and sometimes the sputum of trench fever patients are infective, these should be sterilized in order to avoid the possibility of accidental infection from them.

"8. That in order to prevent trench fever or limit its spread, and thus save man-power for the armies, greater efforts must be made to keep soldiers in general from infestation with lice.

"On account of the great importance of the matter, the following sanitary regulations are advised:

"Exceedingly great care should be taken to disinfect completely all patients as soon as practicable, and particularly upon their entering the hospital. Patients on entrance should be carefully bathed, and subsequently sponged with alcohol. Their clothing and blankets should be removed, and, whether or not lice or ova are found upon them, should be carefully sterilized by moist heat at a temperature not below 70° Centigrade for half an hour, since it is possible for the virus to be still present on the clothing. It should be borne in mind that a man with trench fever may be entirely free from lice at the time that he develops symptoms of the disease. Trench fever patients should at all times be carefully protected from louse infestation, and inspection of them for lice should be made daily. They should be treated in separate wards. As the urine contains the virus and is infective, it should be sterilized during the active stages of the disease. Sputum cups should be provided for patients, and any expectorated sputum and saliva from them sterilized. Officers should regard the systematic destruction of lice as one of the most urgent of their duties, and should exercise every effort to prevent louse infestation among soldiers and to see that any of them infested with lice are promptly disinfected and their clothing sterilized."

He further discusses in some detail the nature of the experiments above referred to, with special reference to the transmission of the disease, and points out that the incubation period of trench fever, when studied experimentally, was shown to be from 14 to 38 days, depending on the dosage and other factors. No reliance, however, can be placed on a study of the apparent incubation period in uncontrolled cases, naturally produced among the troops. The practical value of these incubation period studies lies in the fact that it may be from 10 to 23 days after the last bite by an infected louse before a man will develop trench fever. A man may be quite free from lice at the time of the outset of the symptoms of the disease, and, although a sufferer himself, he is of no danger to others, unless he is in a louse-infected community, so long as his urine and sputum are carefully sterilized.

The remainder of the book contains a careful and systematic detail of the numerous experiments which were the foundation of these conclusions. They enable the writer to examine the evidence and to decide upon the justice of the conclusions formulated by the commission. The work is most creditable to scientific medicine, and is a fresh example of what can be done by the association of a number of observers under the leadership of a competent and experienced head. Similar problems are existing throughout the world, and the need of equally coordinated investigations is pressing.

G. H. W.

The Third Great Plague. By JOHN H. STOKES, M. D. Cloth \$1.50. (Philadelphia: W. B. Saunders Company, 1917.)

Stokes' essay is a most timely one. This book is intended primarily to enlighten the lay mind on the ever-important topic of syphilis. It fulfills more than the author's purpose, for we believe any individual with medical training can profit by a thorough study of it.

The history, nature and course of syphilis; the blood test and treatment; the cure, hereditary aspects, transmission and hygiene

of this ever-increasing plague—so aptly termed—are sketched in a lively, virile, and intelligible style, and best of all in a most understandable manner.

In the chapter on "Mental Attitudes in Their Relation to Syphilis," the moral and personal prophylaxis and the public effort against syphilis are approached and handled with a fair-minded conception of what they entail. A very brief and unprejudiced exposé of the pros and cons of this ever-burning problem are given with a circumspection and judgment which entitle the author to a most respectful hearing.

The book, therefore, is decidedly illuminating; it answers so satisfactorily many of the every-day questions regarding the handling of this, one of our greatest and most serious medical liabilities. It is attractively presented; the style is easy and clear, and the author's attitude on the various moral, social and economic aspects of syphilis are very sane and commendable.

I. R. P.

Syphilis and Public Health. By EDWARD B. VEDDAR, M. D. Cloth \$2.25. (Philadelphia and New York: Lea and Febiger, 1918.)

Following an introduction on the "Importance of Syphilis in Relation to Public Health," together with statistics of mortality, and after a discussion of syphilis as a sanitary problem, the book is divided into four chapters:

1. Prevalence.
2. Sources of Infection and Method of Transmission.
3. Personal Prophylaxis.
4. Public Health Measures.

An appendix is included describing the technic of the Wassermann test of the blood serum; and, in addition, several sections, including the "Control of Syphilis in the Army," "Methods Employed in Some Cities," etc.

This book is a real contribution to the literature of syphilis. Statistics are frequently a "necessary evil" and always open to criticism, but the value of figures in a book of this scope is essential, and therefore beyond the domain of a critical review.

Veddar's discussion of facts and of figures is supplemented by a splendid bibliography, especially on the methods of transmission. This latter chapter is worthy of careful reading. The presentation of the pros and cons of prophylaxis, as well as the discussion on the value of chemical methods of prevention, together with a history of the use of calomel ointment, are splendid features. The author's views on notification, treatment, and especially on the sociological aspects, are rational and worthy of commendation.

This handy volume is well written and well typed. We would recommend it most warmly to the notice of all individuals interested in the medical and (consequently) sociological field of syphilology.

I. R. P.

Diseases of the Skin., By MILTON B. HARTZELL, M. D. Cloth \$7.00. (Philadelphia: J. B. Lippincott Company, 1917.)

With the appearance of another text-book on dermatology, the reviewer naturally looks, among other things, for something new or for a different presentation of facts already known. Dr. Hartzell's book is, in this connection, both satisfying and disappointing.

The subject is handled by the author in the manner usually followed by the every-day text-book. Nothing new is suggested or proposed. One finds the invariable divisions of anatomy, symptomatology, general etiology, etc., followed by the customary division of the dermatoses, according to anatomic characters, hyperæmias, inflammations, hemorrhages, new growths, neuroses, etc.

The size of the book is adequate, but it is neither a short résumé for the student nor an encyclopedic reference treatise for the specialist. Nevertheless, it should prove to be very profitable read-

ing for the general practitioner who is not too deeply concerned with the finer distinctions of diagnosis, pathology and treatment. If considered in this light one finds the book sufficient, and although it presents nothing startling or new in the consideration of general etiology and treatment, it deserves credit for voicing the author's personal views on many subjects. It is unfortunate that the author, after attributing so much well-deserved credit to X-ray therapy, has not incorporated a brief section on this ever-increasing and important therapeutic agent, and also on radium therapy.

With the exception of several worthless colored plates, the photographs and plates are notably splendid; and the photomicrographs in particular—a genuine relief from the almost diagrammatic sketches in the older treatises—brook no criticism. The remarks on etiology and pathology are eminently concise, rational and clear; they are adequately stressed.

There are other outstanding features: the author has avoided much needless discussion; in fact, his somewhat didactic method of presentation is a real advantage; but it is questionable whether the omission of at least a selected bibliography enhances the value of the book. He has certainly done a service in clarifying our knowledge of some dermatoses usually relegated to an obscure grouping. The other brief chapter on sarcoids is ample proof.

It would lead too far to take up the various chapters in critical review. Although the discussion of syphilis appears to be rather scanty, and the pathology somewhat briefly discussed, there are excellent chapters on ringworm and on carcinoma.

The few typographical errors will surely be remedied, together with correction of the spelling of some proper names. The book, therefore, should appeal primarily to the general practitioner; next, to the specialist for a brief review; and lastly, only to the student who, without delving too far, wishes to read and to learn.

I. R. P.

Radio-Diagnosis of Pleuro-Pulmonary Affections. By F. BARJON, Médecin des Hôpitaux de Lyon. Translated by JAMES A. HONEIL, M. D., Assistant Professor of Medicine in charge of Radiography, Yale Medical School. (Yale University Press.)

This volume is the second work published by the Yale University Press on the Williams Memorial Publication Fund—a gift made to Yale University by George C. F. Williams, M. D., a member of the class of 1873, Yale School of Medicine.

Although this translation is a little late in appearing, it arrives at a time when it is most needed. Nothing concerning the X-ray examination of the thorax as yet published has been so thorough as this book. The fluoroscopic examination at the expense of the plate method of study of lesions of the thorax might be mentioned as one of its few weak points.

Frequent reference to other French investigators exclusive of all other nationalities is made and, although the book may have been intended only for use by our French colleagues, it nevertheless must create a little embarrassment to other notables who have so earnestly tried—and, it may be added, not in vain—to elaborate this valuable asset to clinical diagnosis.

The book is divided into five parts with many chapters subdividing each part:

Part I. The Fluoroscopic Appearance of the Normal Chest Shadows when Viewed from All Different Angles.

Part II. The Study of the Pleuræ.

All the different pathological states of the pleuræ are taken up somewhat in detail. Especially interesting is the dissertation on the influences in the production of the curve of Damoiseau. The second chapter deals with circumscribed and encysted pleurisy and is especially clear and well illustrated. The paragraphs dealing with pleurisy of the hilus region with case reports and illus-

trations is a genuine addition to the chapter. The pages devoted to pneumothorax are well illustrated, interesting and instructive.

Part III. Foreign Bodies in the Bronchi.

The metallic foreign bodies and foodstuffs are discussed in detail and the possibility of late and serious pulmonary complications resulting from failure to diagnose them is worthy of mention. The X-ray findings in acute and chronic bronchitis, bronchial stenosis and bronchial dilatation are also instructive. Tracheo-bronchial adenopathy is next studied and a very acceptable and descriptive explanation is given. The various groups of glands are discussed and the best means for observing them on the screen are pointed out. Emphasis is laid upon the fact that too little attention is paid to the study of adenopathy. Illustrations and diaphragmatic drawings also help to complete this part of the work.

Part IV. The Lungs.

The first chapter deals with the fluoroscopic appearances in acute primary and secondary congestion, passive congestion and oedemas. Infarction, its appearance and differentiation from other pulmonary shadows, is particularly clear.

The remaining chapters of Part IV, which are the longest of any, are given over to the study of acute infectious pulmonary processes, chronic pulmonary processes, pulmonary tuberculosis and lung tumors.

Pulmonary tuberculosis is considered under three distinct groups: a. Pulmonary tuberculosis without clinical or stethoscopic signs. (Latent forms.) b. Pulmonary tuberculosis with positive clinical but negative, doubtful or very limited stethoscopic signs. (Early Forms. Period of incubation. Miliary.) c. Advanced pulmonary tuberculosis with evident clinical and stethoscopic signs. (Chronic pulmonary tuberculosis with its many forms.)

Nothing new in the way of diagnosis is offered, but the appearance, development of complications and their appearance fluoroscopically is well pointed out and the total absence of fanaticism certainly adds materially to this greatly discussed topic, the X-ray diagnosis of pulmonary tuberculosis.

Lung tumors complete this part of the book and, aside from mentioning the good illustrations, little need be said.

Part V ends the book and deals with the penetrating wounds of the thorax by war projectiles. A brief clinical and radiologic

entity is given which proves interesting, but certainly not comprehensive enough from a clinical standpoint to be of any material aid to the surgeon or internist in determining the course of procedure in these grave cases. The points discussed in diagnosis and complications are interesting and instructive, but the problems in the localization and extraction of these projectiles are still unanswered.

C. A. W.

Röntgen Technic (Diagnostic). By NORMAN C. PRINCE, M. D. ST. LOUIS: C. V. Mosby & Co., 1917.

This book of 140 pages deals principally with the technic employed in making X-ray plates of different parts of the body.

The descriptive technic is mainly good, but one cannot help feeling that some of the manufacturers of X-ray accessories have used undue influence in advocating their particular products.

In view of the increasing popularity of technicians for the performance of technical duties in an X-ray laboratory the book might have some usefulness in this phase of the work, but when this has been said, no further need for it can be found.

C. A. W.

War Neuroses. By JOHN T. MACCURDY, M. D. With a preface by W. H. R. RIVERS, M. D. (Lond.). 132 pages. (Cambridge: At The University Press, 1918.)

This book consists of observations originally published in the *Psychiatric Bulletin* of the New York State Hospitals, and records the author's conclusions after a brief visit to Great Britain in 1917.

The point of view adopted, with the emphasis on the conflict between the different instincts, that of self-preservation and that of loyalty to the group, and on the adaptive rôle played by the symptoms in the neuroses, is now so widely accepted as not to require special elaboration. The different groups of neuroses, those with predominance of anxiety symptoms, those with predominance of physical symptoms, those where cardiac symptoms are specially in evidence, etc., are discussed in a clear and interesting manner. In special chapters the questions of etiology and of treatment are succinctly dealt with.

C. M. C.

BOOKS RECEIVED

New Jersey. Forty-First Annual Report of the Department of Health of the State of New Jersey, 1917. 1918. 8°. 381 pages. State Gazette Publishing Company, Printers, Trenton, N. J.

Prescriptions of the treaties in Turkey Since the Beginning of the European War. Translated from official Greek documents by Carroll N. Brown, Ph. D., and Theodore P. Ion, D. C. L. 1918. 8°. 72 pages. Published for the American Hellenic Society by Oxford University Press, American Branch, New York City.

Michigan State Board of Health. Forty-Fourth and Forty-Fifth Annual Reports of the Secretary of the State Board of Health of the State of Michigan for the years ending June 30, 1916, and June 30, 1917. 1917. 8°. 243 pages. Wynkoop Hallenbeck Crawford Company, Lansing, Mich.

Amputation Stumps. Their Care and After Treatment. By G. Martin Huggins, F. R. C. S. Oxford War Primers. 1918. 16°. 228 pages. Henry Frowde and Hodder & Stoughton, Oxford University Press, London.

Bipp Treatment of War Wounds. By Rutherford Morison. Oxford War Primers. 1918. 16°. 72 pages. Henry Frowde and Hodder & Stoughton, Oxford University Press, London.

Nursing Technic. By Mary C. Wheeler, R. N. 32 specially prepared illustrations under personal supervision of the author. [1918.] 16°. 265 pages. J. B. Lippincott Company, Philadelphia and London.

The Essentials of Materia Medica and Therapeutics for Nurses. By John Foote, M. D. Third edition, revised, enlarged and reset. Lippincott's Nursing Manuals. [1918.] 8°. 310 pages. J. B. Lippincott Company, Philadelphia and London.

United States, Department of Commerce, Bureau of the Census. Sam L. Rogers Director. Deaf-mutes in the United States. Analysis of the Census of 1910, with Summary of State Laws Relative to the Deaf as of January 1, 1918. 4°. 221 pages. Government Printing Office, Washington.

The Indian Operation of Couching for Cataract. Incorporating the Hunterian Lectures delivered before the Royal College of Surgeons of England on February 19 and 21, 1917. By Robert Henry Elliot, M. D., B. S. (Lond.), Sc. D. (Edin.), F. R. C. S. (Eng.), etc., Lieut. Colonel I. M. S. (retired). With 45 illustrations. 1918. 8°. 94 pages. Paul B. Hoeber, New York.

- Diseases of the Male Urethra, Including Impotence and Sterility.* By Irvin S. Koll, B. S., M. D., F. A. C. S. Illustrated. 1918. 8°. 151 pages. W. B. Saunders Company, Philadelphia and London.
- Clinical Diagnosis.* A Manual of Laboratory Methods. By James Campbell Todd, Ph. B., M. D. Illustrated. Fourth edition, revised and reset. 1918. 12°. 687 pages. W. B. Saunders Company, Philadelphia and London.
- International Clinics.* A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by H. R. M. Landis, M. D. Volume II. Twenty-eighth series, 1918. 8°. 286 pages. J. B. Lippincott Company, Philadelphia and London.
- The Harvey Lectures.* Delivered under the Auspices of the Harvey Society of New York, 1916-1917. By Prof. J. S. Haldane, Dr. F. M. Allen, Dr. Paul A. Lewis, Prof. H. H. Donaldson, Prof. E. V. McCollum, Prof. J. W. Jobling, Prof. John R. Murlin, Prof. F. W. Peabody, Prof. W. H. Howell. Series XII. 1918. 8°. 323 pages. J. B. Lippincott Company, Philadelphia and London.
- The Hodgen Wire Cradle Extension Suspension Splint.* The Exemplification of this Splint with Other Helpful Appliances in the Treatment of Fractures and Wounds of the Extremities and Its Application in Both Civil and War practice. By Frank G. Nifong, M. D., F. A. C. S. With an Introduction by Harvey G. Mudd, M. D., F. A. C. S. With 124 illustrations. 1918. 8°. 162 pages. C. V. Mosby Company, St. Louis.
- A Treatise on Cystoscopy and Urethroscopy.* By Dr. Georges Luys. Translated and edited with additions by Abr. L. Wolbarst, M. D. With 217 figures in the text and 24 chromatographic plates outside the text, including 76 drawings from original water colors. 1918. 8°. 386 pages. C. V. Mosby Company, St. Louis.
- A Manual of Otology.* By Gorham Bacon, A. B., F. A. C. S., assisted by Truman Laurance Saunders, A. B., M. D. Seventh edition, revised and enlarged. With 204 illustrations and two plates. 1918. 12°. 583 pages. Lea & Febiger, New York and Philadelphia.
- Botulism.* A clinical and Experimental Study. By Ernest C. Dickson, M. D. Monograph No. 8. 1918. 4°. 117 pages. Rockefeller Institute for Medical Research, New York.
- University of Michigan.* Transactions of the Clinical Society, October, 1916-October, 1917. Volume VIII. Edited by the Secretary-Treasurer. 1917. 8°. 146 pages. University Hospital, Ann Arbor, Michigan.
- University of Michigan.* Contributions from the Department of Obstetrics and Gynecology. Volume IV, 1915-1918. 4°. Ann Arbor, Michigan.
- Neurological Clinics.* Exercises in the Diagnosis of Diseases of the Nervous System Given at the Neurological Institute, New York, by the Staff of the First Division. Edited by Joseph Collins, M. D. 1918. 8°. 271 pages. Paul B. Hoeber, New York.
- Food Primer for the Home.* Compiled by Lucy H. Gillett. 1918. 8°. 19 pages. Bureau of Food Supply, Association for Improving the Condition of the Poor, New York.
- Clinical Disorders of the Heart Beat.* By Thomas Lewis, M. D., F. R. S., D. Sc., F. R. C. P. [Fourth edition.] 1918. 8°. 120 pages. Paul B. Hoeber, New York.
- The Medical Clinics of North America.* Vol. I, No. 6, May, 1918. 8°. W. B. Saunders Company, Philadelphia and London.
- The Action of Muscles.* Including Muscle Rest and Muscle Re-education. By William Colin Mackenzie M. D., F. R. C. S., F. R. S. (Edin.). With 99 illustrations. 1918. 8°. 267 pages. Paul B. Hoeber, New York.
- Symptoms and Their Interpretation.* By James Mackenzie, M. D., LL. D. [Aber. and Edin.] Third edition. 1918. 8°. 318 pages. Paul B. Hoeber, New York.
- Naval Hygiene.* By James Chambers Pryor, A. M., M. D. Published with approval of the Surgeon General, United States Navy and by permission of the Navy Department. With 153 illustrations. 1918. 12°. 507 pages. P. Blakiston's Son & Co., Philadelphia.
- The Wassermann Test.* By Charles F. Craig, A. M. (Hon.), M. D. (Yale). Published with authority of the Surgeon General, United States Army. Illustrated with colored plates, half-tone plates, and 57 tables. 1918. 8°. 239 pages. C. V. Mosby Company, St. Louis.
- Essentials of Dietetics.* A Text-Book for Nurses. By Maude A. Perry, B. S. 1918. 12°. 159 pages. C. V. Mosby Company, St. Louis.
- Concerning Some Headaches and Eye Disorders of Nasal Origin.* By Greenfield Sluder, M. D. With 115 illustrations. 1918. 8°. 272 pages. C. V. Mosby Company, St. Louis.
- War Surgery of the Abdomen.* By Cuthbert Wallace, C. M. G., F. R. C. S. (Eng.), M. B., B. S. (Lond.). With 26 illustrations. 1918. 8°. 152 pages. P. Blakiston's Son & Co., Philadelphia.
- La Suspension dans le Traitement des Fractures.* Par P. Desfosses et Charles Robert. Préface de M. Pierre Duval. 1918. 12°. 172 pages. Masson et Cie, Paris.
- Surgical Applied Anatomy.* By Sir Frederick Treves, Bart., G. C. V. O., C. B., LL. D., F. R. C. S. (Eng.). Seventh edition, revised by Arthur Keith, M. D., LL. D. (Aber.), F. R. C. S. (Eng.), F. R. S., and W. Colin Mackenzie, M. D. (Melb.), F. R. C. S. (Edin.), F. R. S. E. Illustrated with 153 figures, including 74 in color. [1917.] 16°. 702 pages. Lea & Febiger, Philadelphia and New York.
- A Text-Book of Physiology For Nurses.* By William Gay Christian, M. D., and Charles C. Haskell, M. D. Illustrated. 1918. 12°. 168 pages. C. V. Mosby Company, St. Louis.
- Surgical and War Nursing.* By A. H. Barkley, M. D. (Hon.), M. C., F. A. C. S. With 79 illustrations. 1918. 12°. 208 pages. C. V. Mosby Company, St. Louis.
- Hygiene for Nurses.* By Nolie Mumey, M. D. With 75 illustrations. 1918. 12°. 160 pages. C. V. Mosby Company, St. Louis.
- Nursing in Diseases of Children.* By Carl G. Leo-Wolf, M. D. With 72 illustrations. 1918. 12°. 314 pages. C. V. Mosby Company, St. Louis.
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- Contribution to the Pharmacology of Opium.* 1915-1918. By Dr. David I. Macht, Baltimore, 1918.
- Metropolitan Asylums Board.* Annual Report for the Year 1917. (20th year of issue.) 1918. 8°. 57 pages. London.
- Hygiene of the Eye.* By Wm. Campbell Posey, A. B., M. D. 120 illustrations. 1918. 8°. 344 pages. J. B. Lippincott Company, Philadelphia and London.

- Neuropsychiatry and the War.* A Bibliography with Abstracts. Prepared by Mabel Webster Brown, Edited by Frankwood E. Williams, M. D. 1918. 8°. 292 pages. War Work Committee, The National Committee for Mental Hygiene, Inc., New York City.
- The Medical Association of the Isthmian Canal Zone.* Proceedings of the Medical Association of the Isthmian Canal Zone. Vol. X, Part I, January to June, 1917. 1918, 8°. 149 pages. Published by the Health Department, The Panama Canal. Panama Canal Press, Mount Hope, C. Z.
- Public Health Reports.* Issued weekly by the United States Public Health Service, containing information of the current prevalence of disease, the occurrence of epidemics, sanitary legislation, and related subjects. Vol. 32, Part I, January-June, 1917. 1918. 8°. 1074 pages. Government Printing Office, Washington.
- The Surgery of Oral Diseases and Malformations.* Their Diagnosis and Treatment. By George Van Ingen Brown, D. D. S., M. D., C. M., F. A. C. S. Third edition, with 570 engravings and 20 plates, and a selected list of examination questions. 1918. 8°. 734 pages. Lea & Febiger, Philadelphia and New York.
- Anatomy of the Human Body.* By Henry Gray, F. R. S. Twentieth edition, thoroughly revised and re-edited by Warren H. Lewis, B. S., M. D. Illustrated with 1247 engravings. 1918. 4°. 1396 pages. Lea & Febiger, Philadelphia and New York.
- Genito-Urinary Diseases and Syphilis.* By Henry H. Morton, M. D., F. A. C. S. Fourth edition, revised and enlarged, with 330 illustrations and 36 full-page colored plates. 1918. 8°. 807 pages. C. V. Mosby Company, St. Louis.
- As Introduction to the Mammalian Dentition.* By T. Wingate Todd, M. B., Ch. B. (Manc.), F. R. C. S. (Eng.), Captain, Canadian Army Medical Corps. With 100 illustrations. 1918. 8°. 290 pages. C. V. Mosby Company, St. Louis.
- Radio-Diagnosis of Pleuro-Pulmonary Affections.* By F. Barjon. Translated by James A. Honeij, M. D. 1918. 8°. 183 pages. Yale University Press, New Haven; Humphrey Milford, London.
- Dispensaries, Their Management and Development.* A book for Administrators, Public Health Workers, and All Interested in Better Medical Service for the People. By Michael M. Davis, Jr., Ph. D., and Andrew R. Warner, M. D. 1918. 8°. 438 pages. Macmillan Company, New York.
- The Diseases of Infancy and Childhood.* Designed for the use of Students and Practitioners of Medicine. By Henry Koplik, M. D. Fourth edition, revised and enlarged, illustrated with 239 engravings and 25 plates in color and monochrome. 1918. 8°. 928 pages. Lea & Febiger, Philadelphia and New York.
- Röntgen Diagnosis of Diseases of the Head.* By Dr. Arthur Schüller. Authorized translation by Fred F. Stocking, M. D., M. R. C. With a foreword by Ernest Sachs, M. D. Approved for publication by the Surgeon General of the United States Army. 1918. 8°. 305 pages. C. V. Mosby Company, St. Louis.
- The Human Skeleton, An Interpretation.* By Herbert Eugene Walter. With 175 illustrations. 1918. 12°. 214 pages. Macmillan Company, New York.
- Abstracts of War Surgery.* An Abstract of the War Literature of General Surgery that has been Published since the Declaration of War in 1914. Prepared by the Division of Surgery, Surgeon General's Office. 1918. 8°. 434 pages. C. V. Mosby Company, St. Louis.
- English, French, Italian, Medical Vocabulary.* By Joseph Marie. 1918. 24°. 112 pages. P. Blakiston's Son & Co., Philadelphia.
- Text-Book of Anatomy and Physiology for Nurses.* By Diana Clifford Kimber and Carolyn E. Gray, B. Sc. (Columbia University), R. N. Fifth edition, revised. 1918. 8°. 527 pages. Macmillan Company, New York.
- Vaccines and Sera, Their Clinical Value in Military and Civilian Practice.* By A. Geoffrey Shera, B. A., M. D., B. C. (Cantab.). With an introduction by Sir Clifford Allbutt, K. C. B., M. D., F. R. S. 1918. 16°. 226 pages. Henry Frowde and Hodder & Stoughton, London.
- Tumours, Innocent and Malignant.* Their Clinical Characters and Appropriate Treatment. By Sir John Bland-Sutton LL. D., F. R. C. S. With 383 illustrations. Sixth edition. [1917.] 8°. 790 pages. Paul B. Hoeber, New York.
- Stanford University.* Medical Bulletin No. 5, 1917-1918.
- The Newer Knowledge of Nutrition.* The Use of Food for the Preservation of Vitality and Health. By E. V. McCollum. Illustrated. 1918. 12°. 199 pages. Macmillan Company, New York.
- College of Physicians.* Transactions of the College of Physicians of Philadelphia. Third series. Volume the Thirty-Ninth. 1917. 8°. 518 pages. Philadelphia.
- War Neuroses.* By John T. MacCurdy, M. D. With a preface by W. H. R. Rivers, M. D. (London.) 1918. 8°. 132 pages. University Press, Cambridge.
- Royal College of Surgeons of England.* Calendar of the Royal College of Surgeons of England. August 1, 1918. 407 pages. 8°. Taylor and Francis, London, England.
- The Effect of Diet on Endurance.* By Irving Fisher. 1918. 12°. 55 pages. Yale University Press, New Haven; Humphrey Milford, Oxford University Press, London.
- A Text-Book of Home Nursing.* Modern Scientific Methods for the Care of the Sick. By Eveleen Harrison. Second edition, revised. 1918. 12°. 193 pages. Macmillan Company, New York.
- Dietetics for Nurses.* By Fairfax T. Proudfit. 1918. 8°. 444 pages. Macmillan Company, New York.
- Compendium of Histo-Pathological Technic.* By Emma H. Adler. 1918. 12°. 92 pages. Paul B. Hoeber, New York.
- Mental Diseases.* A Handbook Dealing with Diagnosis and Classification. By Walter Vose Gulick, M. D. Illustrated. 1918. 8°. 142 pages. C. V. Mosby Company, St. Louis.
- Equilibrium and Vertigo.* By Isaac H. Jones, M. A., M. D. With an Analysis of Pathological Cases. By Lewis Fisher, M. D. Adopted as Standard for Medical Division, Signal Corps, Aviation Section, by Surgeon General and Chief Signal Officer, United States Army. With 130 illustrations. 1918. 8°. 444 pages. J. B. Lippincott Company, Philadelphia and London.
- Physiology and Biochemistry in Modern Medicine.* By J. B. Macleod, M. B. Assisted by Roy G. Pearce, B. A., M. D., and by others. With 233 illustrations, including 11 plates in colors. 1918. 8°. 903 pages. C. V. Mosby Company, St. Louis.
- The Rockefeller Foundation, International Health Board.* Fourth Annual Report, January 1, 1917-December 31, 1917. (Publication No. 7.) January, 1918. 8°. 160 pages. New York.
- Information for the Tuberculous.* By F. W. Wittich, A. M., M. D. 1918. 12°. 150 pages. C. V. Mosby Company, St. Louis.
- United States, Department of Commerce, Bureau of the Census.* Mortality Statistics, 1916. Seventeenth annual report. 1918. 4°. 543 pages. Government Printing Office, Washington.

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THE OCCURRENCE OF GASTRIC MUCOSA IN A CASE OF MECKEL'S DIVERTICULUM PRODUCING INTESTINAL OBSTRUCTION

By EMIL GOETSCH

(From the Departments of Surgery of The Peter Bent Brigham Hospital and The Harvard and Johns Hopkins Medical Schools)

The occurrence in the human body of aberrant glandular tissue, at times in places far removed from the mother tissue, is a subject not only of general medical interest and of special interest to the embryologist, but also attracts the attention of the pathologist and surgeon, who frequently meet with abnormalities arising from such aberrant tissue. The purpose of this report is to record such an instance occurring in an interesting case of partial obstruction caused by Meckel's diverticulum in which, at operation, a striking variation was discovered in the mucous membrane of the distal half of the diverticulum. This area of mucous membrane at the tip of Meckel's diverticulum was differentiated strikingly from the proximal mucosa by a sharp line of demarcation and by a difference in color, surface character and in thickness. On subsequent sectioning, this area of mucosa proved to be of the precise character of gastric (fundus) mucosa, containing the typical gastric glands (foveolæ gastricae) composed of the two distinctive types of cells, the parietal and chief, each of which presented their characteristics of morphology and of staining reaction. It is desired further to explain the probable embryological origin of

this gastric tissue in Meckel's diverticulum with a view to throwing further light upon the occurrence of aberrant glandular tissue at the umbilicus and in the remains of the omphalo-mesenteric duct, as reported in the literature.

The case, Hospital No. 623, is that of a well-developed, single young man, 19 years of age, and caterer by occupation. He was born in Ireland and came to America four years previous to his entrance into the Peter Bent Brigham Hospital on August 26, 1913. He was admitted into the surgical clinic of Prof. Harvey Cushing, to whom I am indebted for the privilege of reporting this case. The young man complained of pain in the abdomen and vomiting. No information was obtained in regard to his family or past history which had any bearing on his present trouble except for the fact that six years previously, while he was in Ireland, he was operated upon for what he called a stomach abscess. The details of the condition for which he was operated upon he was unable to give. At that time the abdomen was explored at a point just below the umbilicus and drainage instituted. The abscess healed in a few weeks and the patient made a complete recovery.

ery. Except for this experience he had enjoyed exceptionally good health.

Without going into the details of his present illness suffice it to say that his symptoms began with headache 48 hours before admission to the hospital and were followed in about 36 hours by severe cramps in the abdomen, especially in the lower half and toward the right side. The day before coming to the hospital he suffered severely with vomiting and retching, the vomitus containing large quantities of bile. These symptoms persisted up to the time he came into the hospital. His appetite was poor during the two days of his illness, and his bowels moved once on the day previous to admission. During this same day the patient had a definite fever.

On admission to the hospital he appeared very ill. As a consequence of his excessive vomiting and retching his mouth was exceedingly dry, his tongue red and "beefy" and there was some bleeding of the gums. His temperature was 101.2°, pulse 92 to the minute and his leucocytes numbered 15,000 per c. mm. Examination of the abdomen showed no discernible irregularities, nor were any peristaltic waves seen. There was some fullness present, especially in the lower half. Respiration was entirely costal in type. There was no marked general muscular rigidity, although there was increased tension of the abdominal muscles over the lower half of the abdomen. On deep palpation over McBurney's point slight tenderness could be elicited. Elsewhere there was no abnormal tenderness. On percussion, dullness could be demonstrated in the right lower abdomen and in the flanks. This dullness shifted with change of position of the patient and gave a splashing sound when the overlying abdominal wall was tapped while pressure was made in the flanks. There was evidence, then, of free fluid in the peritoneal cavity. The upper abdomen was markedly tympanic. The evidence of former operation was present in an irregular scar just below the umbilicus, measuring about 1.5 cm. in transverse and 2 cm. in vertical diameter. Rectal examination revealed nothing abnormal. Without entering into further details of the examination it may be stated simply that the diagnosis appeared to be either intestinal obstruction or acute appendicitis with perforation. As the patient's general condition demanded immediate operation, abdominal exploration was advised and readily consented to.

The operation, done about one hour after the patient entered the hospital, was carried out through a right rectus incision. In the peritoneal cavity there was present a fairly large amount of free, serous fluid. Several moderately distended reddish-looking loops of small bowel were seen and also some collapsed grayish loops. Exploration was first made in the region of the appendix. Numerous adhesions resulting from the former abscess and operation had to be carefully separated. After considerable difficulty the appendix, which was coiled back on itself in U-shaped fashion and firmly adherent in the right iliac fossa, was freed and brought into view. It was unusually long, measuring 17-18 cm. in length, of uniform thickness and of fibrous consistency. There was evidence of a moderate chronic inflammation in this region; the appendix, however, was not acutely inflamed. Appendectomy was done. The

condition of the appendix, I felt, could not be held responsible for the patient's present condition and further exploration was made. At once a collapsed small intestine was seen low in the abdomen and pelvis, while numerous overlying, reddish, distended loops of small bowel were seen coming from above. After further search it was found that the division between distended and collapsed bowel was sharply demarcated by a thick, firm, pinkish-white cord, measuring 1.5 cm. in thickness and 6-7 cm. in length, attached at the distal end to the abdominal wall by means of adherent omentum at a point just below the umbilicus and connected at the proximal end with the terminal ileum at a distance proximal to the ileocecal valve, common for Meckel's diverticulum (*cf.* schematic drawing, Fig. 1). Over this cord the loops of small intestine were draped like clothes on a line and had become obstructed. The distal end or tip of the diverticulum was attached to the abdominal wall at the site of the former abscess and operation. Without great difficulty, the distal end together with the adherent omentum was dissected free from the abdominal wall and the base of the diverticulum at its attachment to the ileum amputated and treated in the manner of an appendectomy. Further rapid search revealed no other abnormal findings, such as infection or seriously damaged loops of small intestine, whereupon closure of the abdominal wound was made without drainage. There were no disturbing symptoms following the operation and the patient made a rapid, complete recovery.

In view of the findings at operation it seems likely that the abdominal abscess for which the patient was operated upon six years previously had its origin in a perforation at the tip of Meckel's diverticulum and that simple drainage of the abscess was done through a small incision just below the umbilicus, following which the abscess healed. The possible cause of the perforation will be considered later.

Upon further examination it was found that the diverticulum had a large lumen which at the point of attachment to the ileum measured about three-fourths of a centimeter in diameter. It did not have the appearance of acute inflammation. The diverticulum was then slit open in a longitudinal direction, whereupon a striking appearance was presented by the mucous membrane. The proximal three-fourths of the mucosa had a rather smooth, rolling, slightly folded surface. It was pale-pinkish in color and resembled in this respect the mucosa of the terminal ileum or first portion of the large bowel. The distal one-fourth of the mucosa was considerably thicker and was elevated above the surface of the proximal mucosa from which it was separated by a sharp line of transition. It had, furthermore, a sharp differentiation in color, in that it was of a deep red, cherry hue and its surface was thrown up into large folds, the surface of which again was irregular and granular in appearance. (*Cf.* drawing, Fig. 2, *g. m.*) There was a marked difference also in the thickness of the diverticular wall which, in its proximal portion, was of the thickness of the terminal ileum, while at the tip it was three to four times as thick as the latter. The muscular coat, on the whole, was rather thin, and externally there was a

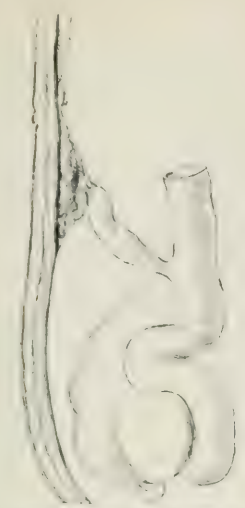


Fig. 1. Muscular stomach, with adherent intestine, projecting to the right, anteriorly, and 20 cm. lower than the umbilicus. (Schematic.) The tumor, 50 mm. in diameter, is situated 10 cm. and 15 cm. from the pylorus and duodenum, respectively.

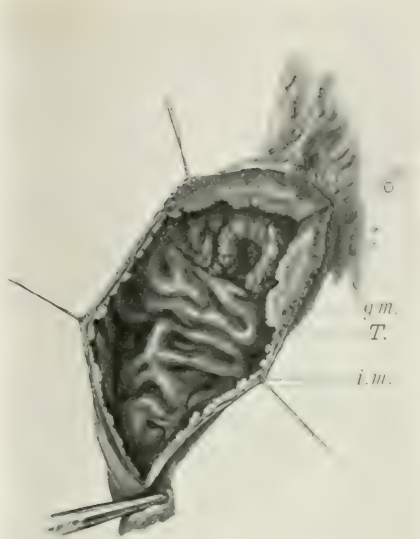


Fig. 2. Muscular stomach, with adherent intestine, projecting to the right, anteriorly, and 20 cm. lower than the umbilicus. The tumor, 50 mm. in diameter, is situated 10 cm. and 15 cm. from the pylorus and duodenum, respectively. (Anatomical.)

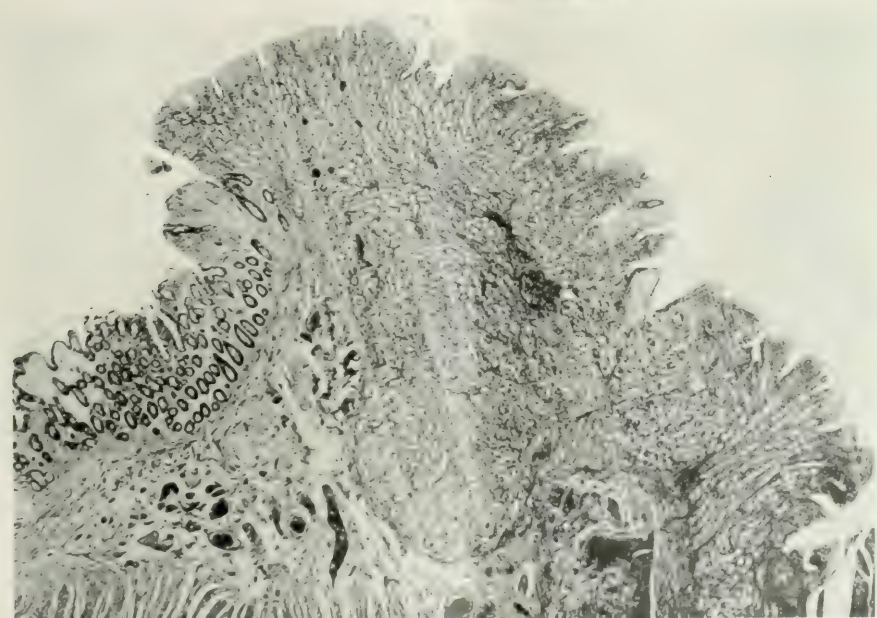


Fig. 3. Low power, microscopic view of the tumor, showing the cellular structure and the presence of the tumor cells. The tumor is a carcinoma, and the cells are arranged in a disorganized pattern. The tumor is situated 10 cm. and 15 cm. from the pylorus and duodenum, respectively. (Microscopic.)



serous peritoneal covering continuous with the serosa of the small bowel itself. At the tip there was a mass of adherent, corrugated-looking omentum which had probably become adherent there at the time of the former abscess and operation. Further examination at the time revealed no perforation nor evident defect in the mucosa at the tip of the diverticulum. The whole specimen was placed in 10 per cent formalin for subsequent study.

Frozen sections were made of the wall of the diverticulum so as to include the transition line (*cf.* photomicrograph, Fig. 3) between the two types of mucous membrane and were then stained in hæmatoxylin and eosin. The proximal, thinner, mucosa (similar to that seen on the left in Fig. 3) resembled in structure that of the duodenum, or in many respects also the ascending and transverse colon; whereas in the thicker, more irregular, distal mucosa (on the right in Fig. 3), at the tip there were seen deep glands which resembled in structure the fundus glands of the stomach and which were composed of two types of cells—the larger, less numerous, bright-red-staining eosinophilic parietal cells and the more numerous, smaller, indifferent-staining chief cells. In order to study in greater detail the two types of mucosa, paraffin sections were prepared. Several additional staining methods were used, namely, cresylecht-violett, the iron-hæmatoxylin method, the acid fuchsin and the neutral gentian methods as recommended by Bensley and the mucicarmine method for the demonstration of mucus in the goblet cells and in the distal goblet zone in the surface columnar cells of the gastric mucosa.

I. STRUCTURE OF THE MUCOSA PROXIMAL TO THE TRANSITION POINT (*T*) (*cf.* FIGS. 2 AND 3)

Sections were made at the line of demarcation or transition between the two adjoining types of mucosa. Fig. 3 represents a low-power photograph of an ordinary section stained in hæmatoxylin and eosin and magnified 24 diameters. The photograph shows the sudden transition from the thinner proximal mucosa, on the left in the photograph, to the thicker, more irregular, distal mucosa on the right. The striking difference in the relative thickness of the two mucous membranes is well shown. A section of the proximal mucosa on the left when observed under the higher power and after staining in cresylecht-violett is seen to consist of a propria containing simple, unbranched, comparatively shallow tubular glands (*cf.* drawing, Fig. 4, of a similar section after iron-hæmatoxylin). The mucous membrane has an irregular surface and forms papillary outgrowths between the openings or crypts of the glands. The lining epithelium is almost uniformly of the tall columnar variety, containing numerous goblet, mucous cells throughout the extent of the mucous membrane. These goblet cells in the neck and depth of the glands are so numerous as to form in places the majority of the cells lining the tubules. Here and there between the swollen goblet cells are seen thin, tall, irregularly compressed, columnar cells—probably discharged goblet cells. Their protoplasm is compact, non-granular and more deeply stained. The cells on the surface are of a low columnar, in places almost

cubical, type, with fewer goblet mucous cells than elsewhere in the glands. In sections doubly stained in iron-alum-hæmatoxylin followed by mucicarmine (the strong stock solution of Mayer), as recommended by Bensley,⁴ the goblet cells contrast strikingly on account of the bright red stain which their irregular, stringy or spongy contents take, showing thus the mucous character of the secretion of these cells. After staining in cresylecht-violett the mucous takes on a faintly purple tint as compared with the remainder of the cell. Near the center of the cell is a denser, more deeply bluish stained zone of cytoplasm separating the mucous secretion of the cell from the basal protoplasmic portion. The nuclei are large, rounded or oval, fairly clear and basally placed. They contain a moderate amount of chromatin and have each a densely stained purple nucleolus. Many of the nuclei, however, are elongated and flattened, due to pressure from adjoining cells; in the smaller cells they are basally placed, while in the discharged cells they have a more central location. The protoplasm of those cells lying between the goblet cells does not contain secretion granules.

Many of these appearances are seen as well in the sections stained after the iron-alum-hæmatoxylin method. Thus in the drawing (Fig. 4) the goblet cells appear unstained, being represented as clear spaces. There are no true villi of the small intestine type. In studying the section further in the oil immersion we find that the cells on the surface have a kind of striated cuticular border. The nuclei of the cells, which apparently rest upon a definite basement membrane, have the same character as those just described in the preceding paragraph. The protoplasm of the tall columnar cells between the goblet cells fails to show any granules which one would consider as the antecedents of ferment secretion.

The propria (Fig. 4) is a loose tissue, containing numerous small blood-vessels and lymphatics, lymphoid cells and connective-tissue cells. In it are also a few smooth muscle fibers from the *L. muscularis mucosæ* running upwards into the mucous membrane prolongations. In one area there is a definite aggregation of lymphoid tissue with a germinating center; in fact, a lymphoid follicle with an outer denser zone of small round cells in the center of which appears a clearer zone with larger cells and richer reticulum. Lymphoid tissue of this kind is seen also in the sections taken from this proximal portion of the mucosa.

The submucosa consists of a layer of loose connective tissue which contains blood-vessels and above which lies the *L. muscularis mucosæ* (Fig. 4). Externally to this again there appears a thick tunica muscularis, consisting of a thick inner circular and an outer longitudinal layer, between which there lies a plexus of nerve tissue. A small portion only of this muscle coat appears in the lower right-hand corner of the drawing (Fig. 4).

Additional sections including both types of mucosa were made of the transition zone (*T*, Fig. 2) and stained in hæmatoxylin and eosin, cresylecht-violett, iron-alum-hæmatoxylin and in mucicarmine. In the mucosa just distal to the transition line (on the right in Fig. 3) the following changes

occur: The proximal duodenal or perhaps transverse-colon type of mucosa rather suddenly changes into a kind of transitional surface epithelium, consisting of two or more irregular cell rows and two different types of cells. The majority of these cells are of a taller type than those lining the intestinal mucosa, and the nuclei, which are irregularly oval or rounded, are more centrally placed and stain in hæmatoxylin a diffuse bluish-purple in which a darker purple centrosome is usually evident. These cells are often flattened and compressed, cylindrical, fusiform or dumb-bell shaped. Each surface cell has a marginal cuticular border and a distal clearer zone separated from the more proximal protoplasmic portion of the cell by a transverse denser cytoplasmic band. In the cresylecht-violett stain the distal clearer zone just described has a rather homogeneous structure and stains a very pale blue, as distinct from the denser blue proximal protoplasm. The nuclei stain a pale violet. In the mucicarmine the distal zone in many instances is stained bright red, showing the presence of mucus. In neither the cresylecht-violett nor in the iron-alum-hæmatoxylin stained sections are any secretion granules apparent in these surface cells.

The cells of the second type in the surface mucosa are usually more deeply situated. These cells are rounded or hexagonal in shape and have a comparatively clear protoplasm. The nuclei are irregularly rounded or oval and deeply stained.

The propria is rich in lymphoid cells, blood capillaries and connective-tissue cells. Numerous mast-cells, so frequently seen in the normal stomach mucosa, are seen here also, and in their cytoplasm the characteristic large red granules, after staining in cresylecht-violett, can be recognized.

Numerous crypts or tubular prolongations are seen dipping down from the surface into the propria. These glands are highly tortuous, especially in their depths, and are lined by two kinds of cells. The majority of them, the chief cells, to use the terminology as applied to the gastric fundus mucosa, are low columnar or cuboidal in shape, with a darker-staining basal zone of protoplasm which has a slightly granular appearance. The lumen border of each cell is relatively clearer and the nucleus is rather large, irregularly rounded or oval, and basally placed. These cells after staining in cresylecht-violett are pale blue, with violet nuclei and bluish nucleoli. Secretion granules do not appear in this stain, but after the iron-alum-hæmatoxylin method, great numbers of black-stained zymogen secretion granules are seen, such as one finds typically in the chief cells of the gastric mucous membrane. A more detailed description of these cells is given later.

The cells of the second type found in these glands are considerably larger than the chief cell just mentioned. They do not, as a rule, touch the lumen of the tubule, as they have a parietal situation and frequently lie between or upon the chief cells just mentioned. In the hæmatoxylin-eosin preparation a cell of this type stains light red or pink in the eosin, as distinct from the chief cell. It has, further, a distinct cell definition and a round, usually centrally placed nucleus, rich in chromatin. Uniformly distributed in its protoplasm can be seen rather large, highly refractile, practically unstained

granules, suggesting in every way the appearance in the typical parietal cell of the stomach. In the cresylecht-violett these parietal cells contrast clearly with the chief cells by staining a faint pinkish-blue, while the latter are darker especially in their basal portions, which are dark blue. The secretion granules in such a preparation are of a violet color. The nuclei are well defined, large and vesicular, and contain relatively little chromatin. Many of the parietal cells are seen to communicate with the lumina of the tubules by a cleft between the neighboring chief cells. In the iron-alum-hæmatoxylin the parietal cells are clearly shown, and in their cytoplasm the secretion granules are seen to be uniformly distributed and stained black. Except for the columnar cells on or near the surface, the mucicarmine fails to show the presence of any mucus-secreting cells in the neck, body or depths of the tubules. A further description of these glands as they occur in a section just beyond the transition line is given below (cf. Fig. 5). In the neck and body of a gland tubule the parietal cells are almost as numerous as the chief cells, while in the depths of the glands the smaller chief cells become more abundant. The appearance throughout in fact is that of gastric fundus mucosa, except perhaps for the greater tortuosity in the tubules than in the glands of the gastric fundus region (cf. Fig. 5).

Just below the mucosa there is a well-developed *L. muscularis mucosæ*, which at one point just beyond the transition line runs upwards, as a papilla or indentation, into the mucous membrane and thereby suggests, together with the thickening in the outer muscle coat, the formation of a sphincter. Just beyond this point, furthermore, the mucous membrane assumes the exact appearance of the fundus mucous membrane and will be described in greater detail later.

The submucosa consists of a loose connective-tissue framework containing blood-vessels in great abundance.

The outer muscle coat is thick, and composed of muscle bundles, not in two definite layers as in the proximal intestinal portion of the section, but running in all directions and intertwining with one another. Numerous nerve fibers can be seen in the outer connective-tissue coat below the parietal covering and also between the muscle bundles. Here also scattered ganglion cells are seen.

II. TYPICAL GASTRIC FUNDUS MUCOSA FROM A POINT JUST DISTAL TO THE TRANSITION LINE DESCRIBED ABOVE (FIG. 5)

At a short distance beyond the transition line between the two types of mucosa the glands of a typical gastric fundus type just described for the transition zone are seen in great numbers. A more detailed description may here be given of the glands as revealed after staining with hæmatoxylin, cresylecht-violett, iron-alum-hæmatoxylin, mucicarmine, neutral gentian and acid fuchsin-methyl-green. The appearance as revealed in the high-power magnification and in oil immersion need only be given here. Many of the findings in repetition of those described as occurring at the transition point are either omitted or only briefly mentioned. The drawing (Fig.

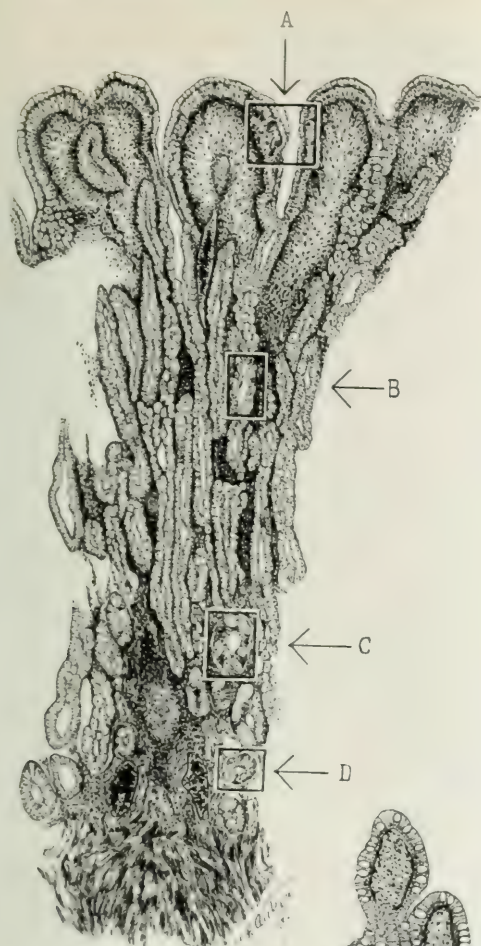


FIG. 1. Diagram of a section of the duodenum showing the various layers and structures. A, mucosa; B, submucosa; C, muscularis; D, serosa. Note the villi, the crypts, the glands, the lymphatics, the blood vessels, and the various cellular elements.



FIG. 2. Diagram of a section of the duodenum showing the various layers and structures. A, mucosa; B, submucosa; C, muscularis; D, serosa. Note the villi, the crypts, the glands, the lymphatics, the blood vessels, and the various cellular elements.

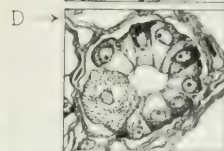
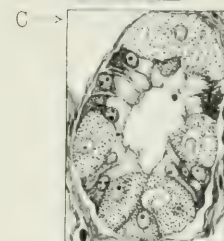
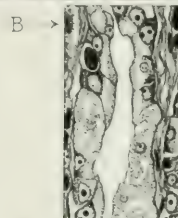
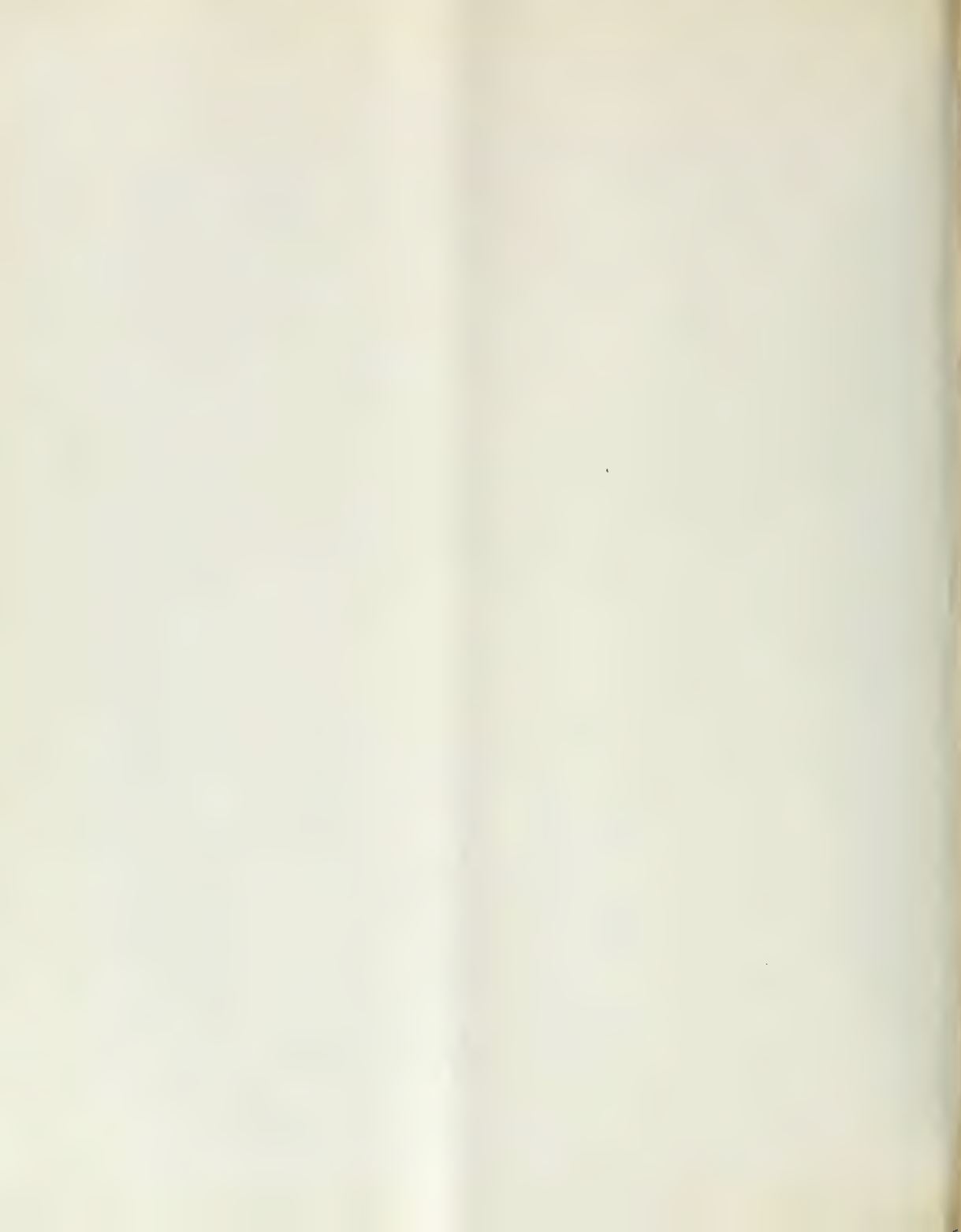


FIG. 3. Diagram of a section of the duodenum showing the various layers and structures. A, mucosa; B, submucosa; C, muscularis; D, serosa. Note the villi, the crypts, the glands, the lymphatics, the blood vessels, and the various cellular elements.



5) illustrates the appearance of a typical gland in moderate magnification, after iron-alum-haematoxylin staining. Four areas squared in this lower power drawing (Fig. 5, A, B, C, D) are represented as seen in high-power oil immersion magnification (Fig. 6, A, B, C, D).

Surface Epithelium.—Numerous crypts or depressions found in the mucous membrane resembling the typical gastric crypts represent the openings or communications through which the more deeply situated glands discharge their secretion into the lumen of the diverticulum. These crypts are lined by epithelium of the surface type, composed of tall, cylindrical cells in a single row or layer (Figs. 5 and 6, A). The large nucleus of each cell with a well-marked nucleolus is round or oval in shape and is usually centrally placed, but often is found above or below the center of the cell. It stains fairly densely by all methods, due to a fair abundance of chromatin. The protoplasm of these cells takes a pale blue stain in the cresylecht-violet and a gray in the haematoxylin and has a spongy structure. Secretion granules are not seen in the protoplasm. In the distal one-fourth of many of the cells there is a clearer zone, in places grossly granular in appearance, having a cup shape and separated from the remainder of the cell protoplasm by a transverse cytoplasmic band. This is the mucus-containing end or zone of the cell, which is not, however, a true goblet cell. True types of the latter were not seen at all in sections from this area. In the cresylecht-violet this mucus stains a pale blue and after mucicarmine a few of the cells on the surface showed this cup-shaped end, or theca, red stained and either grossly granular or stringy in structure. Just below the surface in the crypts the mucus-containing cells are more numerous than on the surface where they are very few in number. Many of the cells have, furthermore, an outer cuticular border.

Glands of the Gastric Fundus Type.—(Figs. 5 and 6, B, C, D.) Into the depths of the crypts empty the secreting glands, one or two, occasionally more, tubules to each crypt. These glands are of the simple tubular variety and occasionally branched. The necks of the glands are quite straight, but in the depths the glands are usually tortuous or convoluted, as indicated by the numerous tubules seen in cross-section in the deeper zone of the mucosa. The glands are in close contact with one another, with almost no intervening tissue of any kind. The propria forms the groundwork or supporting tissue for the glands, surrounds them everywhere and extends upward to the surface epithelium. Under the surface epithelium the propria contains a great many lymphoid cells uniformly and diffusely scattered and fairly abundant. These lymphoid cells, together with numbers of mast-cells, a blood capillary network and some slips from the *L. muscularis mucosae* are also seen extending from the level of the latter upwards between the glands to the surface epithelium. A typical gland may be divided into three portions: the neck (Fig. 5, B), the body (Fig. 5, C) and the depth or base of the gland (Fig. 5, D). The neck of the gland consists of a rather straight tube with a very narrow lumen, lined by two types of cells. The first type is smaller, low columnar or almost cubi-

cal in shape and stains bluish in haematoxylin, with a darker basal zone and a clearer zone bordering on the lumen and containing numerous rather large, black-staining secretion granules. After the neutral gentian technique (Fig. 7) these same cells are stained a violet, especially in the basal portion, and the secretion granules along the lumen border of the cell now stain a dark violet. In the acid fuchsin-methyl-green method (Fig. 8) these granules are faintly green or unstained. These are the characteristic chief cells as seen typically in the gastric fundus mucosa.

The second type of cell is larger, is irregularly rounded or oval, borders on the lumen or is slightly removed from it and covered in part by the neighboring chief cells. This cell is clearer, the protoplasm is stained uniformly pinkish in eosin, pale blue in cresylecht-violet, grayish in iron-haematoxylin, faintly orange in neutral gentian (Fig. 7) and red in the acid fuchsin-methyl-green method (Fig. 8). Scattered uniformly through the protoplasm are definite, large, discrete secretion granules, black in the iron-haematoxylin (Fig. 6, B, C, D), faintly orange in the neutral gentian (Fig. 7) and red in the acid fuchsin methods (Fig. 8). The nuclei are large and vesicular, with relatively little chromatin, are centrally placed and contain a well-marked nucleolus. The cell outlines are sharp. These are the parietal cells, the second characteristic cell of the fundus mucosa of the stomach. The neutral gentian (a neutral combination of the acid orange G and the basic gentian violet) and the acid fuchsin-methyl-green methods were employed to demonstrate the specific staining affinities of the cells and granules of these fundus glands, to add additional evidence to that obtained from the iron-haematoxylin method, that we are dealing with specific secreting gland cells of the true gastric fundus type. The zymogenic secretion granules of the chief cells, having a peculiar affinity for the gentian violet in the neutral gentian stain, are seen colored a dark violet, while the acidophilic granules of the parietal cells have a relatively slight affinity for the orange G and hence appear faintly orange. In the acid fuchsin-methyl-green method, the conditions are just reversed, for which reason this method was employed. We now find that the acidophilic granules of the parietal cells stain a brilliant red in the acid fuchsin, whereas the zymogenic secretion granules of the chief cells are faintly or not at all stained in the methyl-green. The absence of mitochondria, so well demonstrated after osmic-bichromate fixation of the tissue and staining after the acid fuchsin-methyl-green method, is doubtless explainable by the fact that the tissue in this case had remained for a long period of time in 10 per cent formalin. It would have been interesting to study the mitochondria in this tissue as well as the secretion granules, had it been possible to fix some of the original fresh tissue in some other fixing fluids, such as the well-known acetic-osmic-bichromate mixture. The findings described above are well illustrated in the beautiful drawings in color (Figs. 7 and 8) by Miss E. Norris.

Body and Depth of the Gland.—As one observes the gland tubules at greater depths one finds that the same two types of cells are found as described in the neck of the gland tubule.

Here, however, the larger or parietal cell has a truly parietal situation, that it lies removed from the lumen at the periphery of the tubules and communicates with the lumen of the tubules by a cleft between the chief cells. It also occurs oftener. The chief cells show the same characteristics described above. At the base of the cells and forming a kind of basement membrane, the *membrana propria* is evident. Secretion canaliculi in the parietal cells were not definitely seen, due probably to faulty fixation. We have here, then, a type of mucous membrane resembling in every particular, both as to structure and staining affinities, the characteristics of the fundus mucous membrane of the stomach.

A well-developed *L. muscularis mucosæ* is seen, which here and there sends off small, thin prolongations into the overlying *propria* and between the glands. The submucosa has the usual structure of this layer in the intestinal tract.

The tunica muscularis is thick and composed of smooth muscle fibers intertwining with one another in various directions and not definitely demarcated into an outer and inner layer of longitudinal and circular direction. No definite nerve plexuses were recognized.

III. SECTION TAKEN FROM PROXIMAL PART OF MECKEL'S DIVERTICULUM

The structure of the mucous membrane and wall of the diverticulum near to its intestinal attachment does not differ in any important detail from that described above as occurring just proximal to the line of transition (Fig. 4). It was thought that possibly the principal type of mucous membrane, that resembling transverse colon in structure, would assume at the proximal end of the diverticulum the character of ileal mucosa. This is not the case however, for the mucous membrane still resembles that of the transverse colon as described above. There is this difference, however: the mucous membrane is slightly thinner, the folds or plicæ are lower and there is less lymphoid tissue, both diffuse and in the form of follicles. There are more nerve fibers occurring in the submucosa, the tunica muscularis is thicker and more sharply demarcated into an inner circular and an outer longitudinal muscle coat, between which there are more nerve fibers recognizable. Inasmuch as the other findings are similar to those occurring more distally (Fig. 4), a further description need not be given here.

Thus, positive evidence has been advanced by the methods of finer cytological study, that the zone of aberrant glandular tissue in the tip of Meckel's diverticulum is identical in every respect with gastric fundus mucosa. It was thought desirable to make this detailed study of the histological character of this anomalous Meckel's diverticulum for three reasons: In the first place, to establish definitely the fact that we are dealing with a zone of aberrant, but typical, gastric mucosa. This was necessary in view of several reported cases of a somewhat similar nature in which the anomalous or aberrant tissue occurred at the umbilicus and was said to give the appearance of pyloric or simply gastric mucosa, although no histological

examination is reported. For purposes of argument in the explanation of these anomalies it was first of all necessary to advance definite proof that we were dealing with real gastric mucosa. This having been done I feel I have advanced good reasons for believing that the anomalous and aberrant glandular tissues occurring at the umbilicus, in obliterated vitelline cords, and, as in my own case, in Meckel's diverticulum, have a common origin, namely, from the remains of the omphalomesenteric duct. Cases in which pancreatic acini and Lieberkühn's and Brunner's glands have occurred in Meckel's diverticulum have been reported and are given below. Undoubted cases of gastric mucosa, of pancreas and of Lieberkühn's and Brunner's glandular tissue, occurring at the umbilicus in the form of polyps, depressions or fistulæ, have been reported. Several cases are reviewed below in which such aberrant glandular tissue occurred in instances of umbilical fistulæ which were connected with Meckel's diverticulum by a strand or cord. In one or two instances a patent Meckel's diverticulum connected with the umbilicus at which such glandular tissue was found. If we are forced to believe that certain fistulæ at the umbilicus, fibrous cords connecting with Meckel's diverticulum, and the latter itself represent the remains of the vitelline or omphalomesenteric duct, then it would naturally follow that all these anomalous glandular tissues have a common origin. With the discovery of gastric mucosa in Meckel's diverticulum, the chain of evidence of the common origin of these tissues is complete. Additional evidence is then afforded for believing that the umbilical anomalies arise from the omphalomesenteric duct, inasmuch as we know that Meckel's diverticulum represents the remains of the latter structure. A plausible explanation of the embryonic origin of these umbilical anomalies is thus afforded, a fact which is highly desirable in view of the many conflicting explanations with regard to the latter which have been advanced by authors writing on this subject. In the second place, it is interesting to speculate upon the manner in which true gastric mucosa comes to lie in Meckel's diverticulum, so far removed from the mother organ; and in the third place, inflammations, ulcerations, and certain pathological new growths occurring at the umbilicus and in Meckel's diverticulum receive a rational explanation on an embryological basis.

In reviewing the literature in search for accounts of the occurrence of gastric mucosa elsewhere than in its normal location, I have found Chapter VII, pp. 144-158, of Dr. T. S. Cullen's* excellent book on "The Umbilicus and Its Diseases" most helpful. A complete review is given in this chapter of the reported cases of gastric mucosa occurring at the umbilicus.* In the brief account here to be given I have drawn freely from

* The occurrence of intestinal mucosa at the umbilicus, in the form of polypoid growths, with or without depressions or fistulæ, is relatively common as compared with the frequency with which gastric mucosa has been found in the same region. For a good review of the cases of umbilical polyps composed of intestinal mucosa the reader is referred to Cullen: "The Umbilicus and Its Diseases," Chapter VI, pp. 120-143. A complete bibliography on this subject is also given at the end of the chapter.

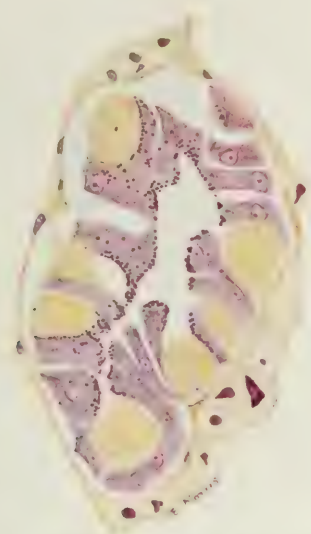


FIG. 7. Drawing of a section of the placenta, showing the chorionic cavity and the umbilical cord. The drawing is a detailed anatomical illustration of a placental section, showing the chorionic cavity and the umbilical cord. The chorionic cavity is a large, irregular space in the center of the placenta, surrounded by chorionic villi. The umbilical cord is shown as a twisted structure entering the placenta from the bottom. The drawing is labeled 'Fig. 7' in the bottom right corner.

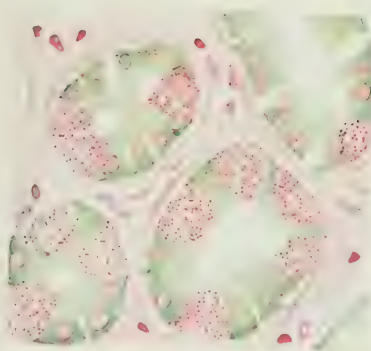


FIG. 8. Drawing of the placenta, showing the chorionic cavity and the umbilical cord. The drawing is a detailed anatomical illustration of a placental section, showing the chorionic cavity and the umbilical cord. The chorionic cavity is a large, irregular space in the center of the placenta, surrounded by chorionic villi. The umbilical cord is shown as a twisted structure entering the placenta from the bottom. The drawing is labeled 'Fig. 8' in the bottom right corner.



this review. Cullen (p. 145) classifies the umbilical abnormalities in which gastric mucosa was found into three types, thus, for example:

I. An umbilical polyp attached to the umbilical depression by a short pedicle.

II. An umbilical polyp with a cystic cavity opening on the surface of the polyp.

III. An umbilical fistula with or without a small projection. Fig. 9 will serve to illustrate the second type.

I. A most interesting example of the first type was described by Tillmanns²⁷ in 1882. In a boy, 13 years of age, there was found at the umbilicus a pedunculated tumor, the size of a walnut, bright red in color, without a central opening and covered with mucosa. After a meal had been eaten, the tumor would swell perceptibly, while the mucosa became redder and thicker. The secretion on the surface of the polyp had a tenacious mucoid character. Whenever the tumor was irritated the flow of secretion was increased so that at such times



FIG. 9.—A long umbilical polyp with a central fistulous opening, a remnant of the omphalomesenteric duct. (Schematic, after Cullen, p. 156.) This is an unusual type, the polyp being shorter and more sessile. A few instances are reported in which the lining mucosa was shown to be of gastric character. There is no connection between the umbilical polyp and the small intestine in this type of polyp.

2 to 3 c. c. of fluid could be collected in 15 minutes. The secretion was acid in reaction, digested albumen, and upon chemical examination was found to resemble normal gastric juice. Upon microscopic examination by Weigert the mucosa was found to have a structure similar to that of the pyloric region of the stomach. On account of its digestive action the secretion of the tumor had caused a maceration of the skin in the vicinity of the umbilicus. Histological examination of the mucosa of the tumor showed this to be similar in structure to pyloric mucous membrane. Tillmanns then explains the condition by showing schematically how a diverticulum of the stomach may be included in the umbilical cord as a prolapse of stomach wall through the umbilicus just as the ileum may do. This explanation will be considered again. No connection with the stomach or other organs was found.

Although the literature upon this subject is scanty, a few subsequent reports of gastric mucosa occurring at the umbilicus were found. Thus, umbilical polypi with a covering of gastric mucosa have been described by van Heukelom²⁸ (1888), Reichard²⁹ (1898), Strada³⁰ (1903), and Minelli³¹ (1905).

In van Heukelom's case, a child two and one-half years of age, a tumor the size of a hickory-nut was found in the umbilical depression. It was red in color and had a granular,

moist surface and was attached by a thin pedicle. The latter was divided and the tumor removed. On microscopic examination the tumor was seen to consist of an inner portion composed of muscle, connective tissue and vessels, and an outer portion or cortex 2 mm. in thickness and consisting of a mucous membrane with long gland tubules, some interstitial connective tissue and some lymphoid tissue at the base of the glands. The latter resembled intestinal glands of the Lieberkühn type. (Van Heukelom's explanation for this finding is given below.) Van Heukelom refers to 12 cases of this kind reported in the literature, his own being the 13th case. He feels that there doubtless are many more which have been reported under the diagnosis of "umbilical granuloma" and have not been examined further. Most of these granulomata when examined have been found to contain epithelium and glands of intestinal type. In these cases there is no mention made of gastric mucosa.

In a further study of the occurrence of gastric mucosa at the umbilicus and with particular reference to Tillmanns' case and his explanation of it, namely, that the gastric mucosa is derived from a gastric diverticulum, van Heukelom examined a number of human fetuses with this point in view. In one of his fetus cases he found a nodule of mucous membrane at the tip of Meckel's diverticulum constricted off from the lumen of the latter. On microscopic examination this nodule was found to resemble the pyloric mucous membrane of this same fetus. The epithelium was very regular, composed of long cylindrical cells with refractile protoplasm and basally situated nuclei. There were no goblet cells. The mucous membrane of the diverticulum, on the other hand, and of the ileum itself was of an entirely different character, namely, intestinal in type. Van Heukelom attempts to explain the origin of this heterotopic mucous membrane, a matter which we shall again consider. It is to be emphasized here that this piece of gastric mucosa was constricted off from the cavity of the diverticulum and in no way communicated with it.

Reichard reports the case of a boy five years old who presented a tumor, the size of a hickory-nut, in the umbilical region, which had a small fistulous opening and from which a clear fluid escaped. There had been a "weeping navel" since birth. At operation the umbilicus was circumscribed, the peritoneum was opened and a cystic, bluish, demarcated tumor was seen, from which a thin stalk ran upwards into the abdominal cavity. The stalk, which was very delicate and could not be followed, was divided. The tumor with the surrounding area of macerated skin was excised. Closure was made of the peritoneum and abdominal wall and the patient made a good recovery.

The cavity of the tumor was lined with a mucous membrane which, when microscopically examined, was seen to resemble the gastric type. No further histological description is given and no statement is made as to whether it was clearly of pyloric or fundus character. Reichard is reminded of the case of Tillmanns, except that in his own case the condition had not gone on to evagination and prolapse of the tumor. He was inclined to believe in the theory of Tillmanns, namely,

that this mucous membrane is derived from a diverticulum of the stomach, and that due to the rotation and further development of the stomach there is a twisting and later obliteration of the cord of communication with the stomach. Siegenbeek van Heukelom, as we shall see, is opposed to this view.

Strada reports the case of a young woman of 20 who had a tumor at the umbilicus covered with mucosa. On microscopic examination this mucosa was seen to consist of cylindrical epithelium and glands of the pyloric type.

Minelli describes an adenoma occurring at the umbilicus presenting a picture of gastric adenoma.

II. A case of the second type, namely, an umbilical polyp with a cystic cavity opening on the surface of the polyp, has been described by Roser²² (1887) in a boy one and one-half years old. A bright red swelling was found at the umbilicus. Opening on the surface of this swelling, which, as stated, belongs to the second type, was a cystic cavity 1 cm. in diameter. The case was very much like that reported by Tillmanns. The secretion from the umbilicus digested the surrounding skin area, was acid in reaction and was responsible for a considerable induration and a red granulation-formation around the opening. The walls and mucous membrane of this cavity were excised. A secondary cauterization had to be done three weeks later on account of incomplete removal. A detailed description of the structure of the mucosa is not given, mention being simply made that the closely aggregated tubular glands, between which there was a good deal of muscle tissue, resembled in every way gastric mucosa. There is no mention made of a serosa nor as to whether the glands were of the fundus or the pyloric type. Roser was inclined to accept the explanation of Tillmanns for this occurrence, namely, that a portion of gastric mucosa had been constricted off from the pyloric region at a time when the stomach had a vertical position and the pylorus was supposed to be nearer the umbilicus. It is hardly necessary to state, as will be explained in further detail below, that this assumption does not suffice, for it is well known that the pylorus in infants and very young children is in no such proximity to the umbilicus, inasmuch as the large liver separates the pylorus and the stomach from the anterior abdominal wall.

III. Fistulous tracts occurring at the umbilicus and containing gastric mucosa have been described by von Rosthorn²³ (1889), Weber²⁴ (1898), Lindner²⁵ (1898), Lexer²⁶ (1899) and Denucé²⁷ (1908). These belong to the third type of cases mentioned above.

Von Rosthorn reports the case of a boy seven years old who had an umbilical fistula. Its presence was first recognized when the cord dropped off. After this a red papule formed which secreted watery fluid and into which a sound could be introduced for a distance of 2 cm. There was a continuous flow of this secretion which amounted to 5 c. c. in 24 hours. It was acid in reaction, slowly digested albumen and did not positively contain free hydrochloric acid. The fistula was excised and the patient was well in 10 days.

On microscopic examination of the tissues from the depths of the tumor, gland lobules were found which reminded one of parotid gland, whereas the branched tubules resembled pyloric glands of the stomach. Von Rosthorn assumed that the acid reaction of the secretion was due to zymotic external influence which had altered the original alkaline reaction. Lieberkühn's glands were also found in the fistula. von Rosthorn offers and accepts the explanation of Siegenbeek van Heukelom for the occurrence of his findings.

In Weber's case there was found in a boy three years old a small red tumor at the umbilicus from which a fistula led downwards for a short distance. From this fistula flowed a watery secretion which contained mucous shreds, but never intestinal or gastric contents. The secretion amounted to half a wineglassful in 24 hours. At meal times the secretion was increased and then often accompanied by a colicky pain. A digestion ulcer had formed around the fistulous opening at the umbilicus which was one-half of a centimeter in diameter. This secretion was alkaline to litmus. Weber felt that the secretion of the tumor was increased during digestion probably by a reflex action through its nerve supply which he thought was doubtless the same as for the normal stomach, for, as we shall see, he felt that the tumor was derived from the stomach by a process of diverticulum-formation. This is in keeping with Tillmanns' view.

The fistulous tract with the surrounding macerated skin was excised. After the peritoneum was opened a thin cord was found leading from the inner end of the tract to the under surface of the liver, but without attachment to either stomach or intestine. A cystic bluish tumor was found at the umbilicus. The stalk was divided, the tumor extirpated as mentioned and closure was made, followed by recovery of the patient.

The cavity of the tumor was lined with a thick mucosa which was of the pyloric type. The columnar surface epithelium was seen to dip down to form glands which were made up of only one kind of cells. There were no chief and parietal cells as in the fundus region and no goblet cells, no villi and no glands or follicles of the Lieberkühn type. There was an *L. muscularis mucosæ* and outside of this a longitudinal and circular muscle coat and a thick serosa. Weber felt that from the gross and microscopic appearances it was safe to assume that he was dealing with normal stomach mucosa from the pyloric region. He felt, also, that the cord passing to the under surface of the liver represented the remains of the umbilical vein. Weber was inclined to the view of Tillmanns, that this fistula and tumor represented a portion of the diverticular stalk from the pyloric region and had become constricted off at the umbilicus.

Lindner, in the discussion of a case of extirpation of a persistent ductus omphalomesentericus reported by Körte in 1898, reports a case of his own in which there was a small, reddish papule at the umbilicus in a boy three years old. For some weeks or even months there was a secretion from this fistula and around it there was a large area of digestion of the abdominal wall. A sound could be introduced into this fistula

for a short distance. At operation a tumor was found, the size of a walnut, behind the umbilicus, which connected in no way with the intestine. From the upper pole of the tumor there was a fine connective-tissue strand running to the under surface of the liver in the region of the incisura. There were no vessels palpable in this cord, which seemed to have no importance whatever. The tumor was excised and was found to be lined by mucous membrane of the pyloric type. Lindner states that cases of this kind are extremely rare and difficult of explanation. He refers to the cases reported by Tillmanns, but does not agree with Tillmanns' explanation of their occurrence. He states that there was no evidence in his case that the tumor had any connection with a diverticulum or former prolapse of the stomach. Lindner did not attempt to explain the occurrence further.

Lexer's patient was a child one year old with a congenital umbilical fistula around which the skin was macerated. The fluid secreted by the fistula was clear, tenacious and acid in

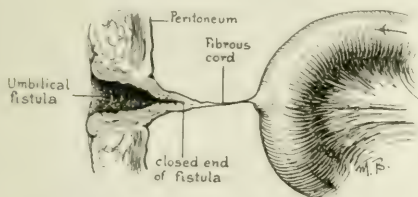


FIG. 10. Persistence of the outer end of the omphalomesenteric duct in the form of an umbilical fistula attached to the small bowel by a fibrous cord. (Schematic, after Cullen, p. 156.) This is the type of remnant of the omphalomesenteric duct described by Lexer. In the latter's case, however, there was a blind fistula at the umbilicus leading downwards a short distance and also a fistulous tract leading from the small intestine through the fibrous cord or obliterated Meckel's diverticulum. The two fistulous tracts, however, did not communicate. The outer umbilical fistula was lined by gastric mucosa and the inner or proximal fistula by intestinal mucosa.

reaction and chemically resembled gastric juice, in that it readily digested egg albumen and fibrin. At operation the fistulous tract was found to have a cord of attachment, as thick as a lead pencil, to the convexity of the small bowel. The cord was amputated from the intestine and the fistulous tract excised. The child made a rapid recovery. The proximal or inner end of the cord, which was attached to the intestine, evidently represented Meckel's diverticulum (Fig. 10). The extirpated fistulous tract had a rather wide opening at the umbilicus and also at the intestinal end, although it was not completely patent throughout its whole extent. The external fistula was one and one-half centimeters in depth. The specimen was thus divided into two parts. The proximal larger section, which communicated freely with the bowel, had a mucous membrane very similar to that of the intestine and of the type generally found in Meckel's diverticulum. Lieberkühn's glands with numerous goblet cells and individual lymph follicles characterized this mucosa. In the original, a plate of a low-power drawing is shown of the histological appearance which resembles my own case, the mucous membrane appearing very much like transverse colon in many respects. The appearance, as shown by section, of the external or umbili-

cal portion of this fistula was very different. The mucous membrane was of the pyloric type, as similarly described by von Rosthorn and Lindner. The epithelium was tall and cylindrical and the protoplasm highly refractile. The nuclei were basally situated and there were no goblet cells. In the depth there was to be seen a richly developed zone of tubular glands connected by numerous crypts with the lumen of the fistula. In general, then, the whole structure of the mucous membrane resembled that of the pyloric region of the stomach. This structure was not as regular, however, as in the normal structure. In the original, a second plate is shown to illustrate this mucosa. External to the mucous membrane there are the usual muscular layers. For a short distance the lumina of the two segments overlapped one another, so that in a single section taken at this point one could see both types of mucous membrane: the intestinal, belonging to the proximal fistula or cavity, and the pyloric type, corresponding to the external or distal fistula. In the depth there was only an imperfect cellular connection between these two types of mucous membrane. At this point there was a mixture of the two types of mucous membrane and Lexer believed that the outer fistula was formed originally, by a constricting process, from the original diverticulum of Meckel. The findings, as a whole, Lexer believes, allow of no other explanation than that there is a complete persistence of the ductus omphalomesentericus, whose outer portion, probably as a result of very early separation, is subjected to a different evolution of its mucous membrane than that portion of the fistulous tract which connected with the intestine, namely, Meckel's diverticulum.

In explanation of the similarity of the secretion from the outer portion with that of gastric juice, Lexer was unable to give any satisfactory facts and referred to the rather unsatisfactory attempts at explanation by van Heukelom and von Rosthorn. Lexer was more inclined to believe that these formations arose from rests of the original omphalomesenteric duct and Meckel's diverticulum rather than from gastric diverticula, even though there was lacking the anatomical connection between the umbilicus and Meckel's diverticulum.

In order to feel that the gastric mucosa at the umbilicus was derived from the same mucosa or from the same structures from which Meckel's diverticulum develops, Lexer said he would like to see a case in which there was a preservation of the connection between the gastric mucous membrane at the umbilicus and a Meckel's diverticulum. My own case shows that even without such an anatomical connection gastric mucosa is found in Meckel's diverticulum and thus affords additional proof that the cases of gastric mucosa at the umbilicus have an origin similar to that of Meckel's diverticulum.

Denné described in a boy 21 months old a congenital fistula at the umbilicus from which there was an abundant flow of secretion which was ordinarily colorless, sometimes slightly hemorrhagic, and which gave an acid reaction and upon chemical examination was found to be practically identical with gastric juice. There was digestive action on the skin around the umbilicus. The microscopic examination of the fluid revealed nothing of importance. Free hydrochloric acid was

present. By means of a sterile pipette 3 c. c. of secretion were collected and examined chemically. The principal findings included demonstration of the presence of albumen, peptone and free hydrochloric acid. The fluid digested coagulated albumen. He concluded, then, that the secretion must be considered a kind of gastric juice. At the operation the fistulous tract was removed without necessitating the opening of the peritoneal cavity. The peritoneum was transparent and it was possible to see, a little to the left of the deeper attachments of the fistula, a cylindrical cord which, at its proximal or inner extremity, was connected with one of the intestinal loops (Fig. 11). It was at once recognized that this cord represented Meckel's diverticulum and connected at its distal extremity with the umbilicus. The diverticulum was then exposed and amputated at its base. The child made a good recovery.

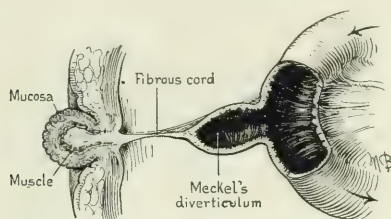


FIG. 11.—An umbilical polyp connected with Meckel's diverticulum by a fibrous cord. (Schematic, after Cullen, p. 121.) This is the type of remnant of the omphalomesenteric duct which was described in Denucé's case. In the latter, however, the umbilical polyp had a central fistula which was lined by mucosa of the fundus type. Remnants of practically the whole of the omphalomesenteric duct are present here. The outer end is represented by the umbilical polyp, the central portion by a fibrous cord and the inner end by Meckel's diverticulum. The latter had the usual intestinal type of mucosa.

The tissue removed was preserved in formalin. The specimen consisted of two parts: the outer fistulous part attached to the external surface of the peritoneum and the inner part or segment consisting of Meckel's diverticulum attached at its distal extremity to the inner peritoneal surface. A section from the outer fistulous part showed the mucous membrane to have the characteristic structure of gastric mucosa of the fundus type. The surface cells were tall, cylindrical in type, and filled with mucus. In the connective tissue there were some fibroblasts, mast-cells and eosinophilic cells. The superficial tubules were continuous below with the true peptic glands. The latter were lined with clear cells containing zymogen granules and a second type of cell, the parietal cells. These were very numerous in the depth of the cul-de-sacs, but less abundant in the deeper portions of the gland tubules. The eosinophilic cells and the mast-cells were also found in the deeper portions of the glandular zone. In the corium true lymphoid nodules with germinating centers were present. The muscular layer on the outside was very thick.

In brief, then, Denucé felt that he was dealing with a gastric heterotopy in the form of an isolated small cul-de-sac or fistula at the umbilicus, plainly and fully functioning. Before discussing further his own case he then refers to some previous observations on the development of our understanding of the

peculiar histology of congenital umbilical fistula of the so-called pseudo-pyloric type, which is extremely rare.

Finally, it may be well to refer briefly to the case described by Salzer^{28a} (1904) of a patent diverticulum (Fig. 12), which in the free abdominal portion showed normal characters of the intestinal mucosa. In the prolapsed portion at the umbilicus, however, there were found glands resembling in structure the cardiac glands of the stomach. In the histological description of these glands he says the cells of the gland tubules are clear, finely granular, polygonal in shape and have a basal nucleus and some affinity for eosin.

In explanation thereof he suggests that, in the closure of the abdominal cavity, for some reason or other, there is a partial or complete cessation in the evolution of the vitelline duct and that thereby the entoderm is irritated or stimulated to

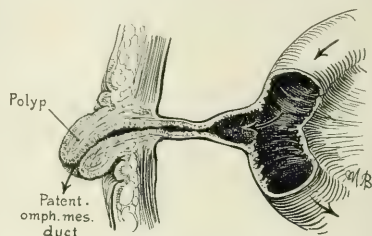


FIG. 12.—A patent omphalomesenteric duct with a polypoid formation at the umbilicus. (Schematic, after Cullen, p. 190.) This represents the type of case described by Salzer. The lumen is continuous through the umbilical polyp, through the persistent omphalomesenteric duct, and communicates with the small intestine.

a variable differentiation, so that there is a development at one time of intestinal mucosa, at another time of gastric; again, there may be produced parotid gland or even pancreas. He says, furthermore, that these pathological pictures are always to be found at the distal end of the remnants of the vitelline duct, in fact, just at that point where the incomplete involution of the vitelline duct is so apt to be found. There have been many different views in explanation of the origin of these aberrant tissues at the umbilicus, with particular reference to the occurrence of gastric mucosa. Before entering upon these, however, it will be helpful to review briefly the embryological evolution of the omphalomesenteric duct. In this way a clear conception can be had of the probable origin of a large number of anomalous conditions which one finds at times at the umbilicus and in its neighborhood.

The vitelline or omphalomesenteric duct represents in fetal life the communication between the intestine (ileum) and the yolk sac. The yolk sac in time develops into the umbilical vesicle. Ordinarily, at about the seventh week to the tenth week the yolk stalk, which connects between the ileum and the umbilical vesicle, separates from the intestine. The latter, which at first lies in part in the umbilical cord, retracts into the abdominal cavity and thereafter there is no further indication of the original connection between the intestine and the yolk sac. If the separation of the intestine from the yolk stalk is delayed or fails to

occur at all, then various resulting anomalies are found in the region of the umbilicus at the time of birth or even later in life. The slightest persistence of the vitelline duct is represented by a thin connective-tissue strand extending from the umbilicus to the ileum. This strand is of little interest aside from the fact that occasionally intestinal obstruction may be produced by it. The fullest degree of persistence of this structure is represented by complete patency of the duct, thus establishing a free communication between the umbilicus and the intestine. From a condition of this kind there develops the well-known type of congenital umbilical fecal fistula, numerous cases of which have been reported. Through such a fistula a portion of the bowel wall or even a loop or more of small bowel may prolapse. Between these two extremes there are all possible transitions. The most common partial persistence of the vitelline duct is that of the well-known finger-like diverticulum of Meckel, which is usually entirely separated but may be connected with the umbilicus by a few fine strands of connective tissue. Such cases are also numerous. A diverticulum thus attached to the umbilicus may cause various types of fetal strangulations, torsions and obstruction. At other times, this duct connecting between the umbilicus and the intestine becomes obliterated at both the umbilical and the intestinal extremities with an intervening lumen lined by a cylindrical epithelium and containing more or less secretion. From a remnant of this kind arise the well-known cysts or enterocystomata. Again, the duct may remain open at the umbilicus and become obliterated within the abdominal cavity. This type of persistence gives rise to umbilical fistulae, tumors and cysts. These may be opened externally at the time of the ligation of the umbilical cord or through umbilical inflammation. Again, there may be a nodule of mucous membrane with or without a lumen and constricted off from the tip of Meckel's diverticulum with which it thus has no communication. Both structures, however, evidently arise from a partial persistence of the original vitelline duct.

We might consider now the theories and views which have been advanced to explain the occurrence of aberrant glandular tissue at the umbilicus and which concern particularly those cases of gastric mucosa reported above.

The first view was that of Tillmanns (1882), namely, that in the cases exhibiting gastric mucosa at the umbilicus in the form of a tumor or fistula we are dealing with remnants of gastric diverticula which have been preserved at the umbilicus, but which have severed their former connections with the mother organ. This view was accepted by Reichard, Roser and Weber. The last, particularly, was a firm believer in this probable origin of the aberrant gastric tissue, and in his report in 1898 explains in detail the mechanism of this formation. As it was impossible for me to get Tillmanns' original article I have quoted largely from Weber's article which follows in general the views of Tillmanns. According to this view, then, there occurred in early fetal life a herniation of the stomach at the umbilicus, which herniation was still connected with the stomach by a kind of diverticulum and that this diverticulum was opened at the time of birth. The question which Weber

now puts to himself is this: How does a gastric diverticulum or herniation come to lie in the first portion of the umbilical cord? His explanation is as follows: In the youngest human embryos which had been examined up to his time, and which were from 14 to 18 days old, the intestine has not yet become a more or less closed tube, but communicates by a rather wide stalk with the yolk sac. Gradually the yolk sac develops into the umbilical vesicle, which is connected by means of the vitelline duct with the subsequent tubular intestine. The vitelline duct becomes a portion of the umbilical cord and later obliterates. The bowel retracts into the abdominal cavity and all connection with the umbilical cord disappears. Up to this point the presence of a portion of the intestine in the beginning of the umbilical cord is a physiological occurrence. If separation of the vitelline duct from the intestine is delayed, then traction within the umbilical cord is exerted upon the intestinal tract and the intestine remains as a normal content of the first portion of the cord, thus producing an umbilical herniation with small intestine as its contents. If this herniation remains it can be readily overlooked by the physician or the midwife, and at the time of ligation of the cord it may be opened so that a fistula may rise from which the child generally dies as a result of complicating peritonitis. On the other hand, such a hernia may be only a temporary occurrence and subsequently, after separation of the vitelline duct, the bowel may retract into the abdominal cavity. In a case of this kind a dilated ring persists at the umbilical opening and thus predisposes to a potential hernia. In this manner a diverticulum of the stomach might enter the umbilical opening, or even without assuming a delayed separation of the vitelline duct such a herniation is conceivable if one imagines the stomach held in application against the umbilical opening by the presence of adhesions.

The second question which Weber asks himself is this: Why is it that there is no tract or strand connecting with the stomach; in other words, why is it that the prolapsed piece of mucous membrane appears as an anlage entirely separated from its point of origin? He believes that there are processes of constriction during the period of development which play a rôle if Tillmanns' theory is at all correct. Thus, if we assume that in an early developmental period there is an attachment between the first portion of the umbilical cord and the stomach, then, as a result of this, traction is exerted upon the stomach as against the traction of the mesentery. The stomach is drawn out into a diverticulum and the connection between the adherent portion and the stomach proper is narrowed down to a very small duct. In addition to this, there are the subsequent changes of position to which the intestinal tract and the stomach are subjected in their further embryological development. Originally the stomach is formed as a fusiform dilatation of the otherwise uniform intestinal tract and has a vertical position. Its long axis becomes transverse and the pylorus comes to lie high on the right and the cardia moves to the left. The portion to the left then develops as the fundus. In addition there is also a torsion of the long axis, so that the left surface becomes anterior and the right

posterior. The mesentery also makes these twists and must therefore alter its length and form, thus creating the bursa omentalis. If we now assume that abnormal adhesions have held the stomach wall in apposition with the region of the umbilicus, then this change in position can readily cause a narrowing of the duct-like connection between the umbilical herniation and the stomach, resulting in the formation of a twisted cord which in time obliterates and finally disappears entirely. Assuming these facts as a plausible hypothesis, Tillmanns and his adherents endeavor to explain the occurrence of gastric mucosa at the umbilicus as a form of ectopia ventriculi. Against this view van Heukelom takes a decided stand.

Van Heukelom, whose view was accepted by von Rosthorn, believes that these aberrant growths at the umbilicus represent remains of the vitelline duct and arise in a manner which he explains as follows: In the second month of fetal life the intestine still forms a loop which is to be found in the umbilical cord. The tip of this loop represents the point from which the ductus omphalomesentericus is constricted off. In the third month this intestinal loop retracts and then the intestine lies free in the abdominal cavity. If we now assume that this diverticulum or loop, for some reason or other, does not retract at its proper time on account of the tension of an unobliterated vitelline duct, then the portion of the diverticulum connecting with the intestine may be pulled away, and being thus entirely separated from the latter comes to lie isolated at the umbilicus. In this manner we have the beginning of our ectopia. If now this mucous membrane and musculature of the open diverticulum at the umbilicus continue to grow while the surrounding umbilical structures retract, then the former will evaginate and in this fashion, in time, a tumor forms, which is covered with mucous membrane. Van Heukelom refers to 12 cases of this kind which he has collected and gives reference to them, his own being the 13th. There are probably many more which have escaped notice because they are classified under umbilical granulomata without further report as to their histology. Many of these aberrant tumors at the umbilicus have been shown to contain intestinal glands and epithelium. In these 13 cases there is no mention made of gastric mucosa.

As already mentioned, van Heukelom described a case of his own of gastric mucosa occurring at the tip of Meckel's diverticulum and feels that there is a uniform origin for all the various aberrant tissues found at the umbilicus. There is a general consensus of opinion that these tissues are derived from the tractus intestinalis, but as to what part of the tract represents the mother organ there is a great difference of opinion. Van Heukelom, in the first place, answers what he considers the erroneous explanation of Tillmanns and Roser, namely, that umbilical gastric mucosa represents a portion constricted off from the early fetal stomach at a time when the stomach is supposed to lie in the vertical position, in close proximity to the umbilicus. Van Heukelom examined a series of fetuses with the purpose of determining the probability of such an occurrence. He concludes that it is impossible to

believe that gastric diverticula can thus be formed, for the reasons that the enormous liver occupies the space between the umbilicus and the deeper lying pylorus and relatively takes up more and more room, the younger the embryo. There is no connection between the pylorus and the umbilicus, but on the contrary there is always a wide separation between them. On the basis of his findings in one of his fetus cases, namely, of a portion of gastric mucous membrane at the tip of Meckel's diverticulum and separated from it, and the finding in Meckel's diverticulum itself of the usual intestinal epithelium, he constructs his theory for the explanation of these variations in histological differentiation.

Two questions, he says, now arise: Firstly, how can one explain the great difference between the epithelium of the distal portion separated from the diverticulum and that of the proximal portion of Meckel's diverticulum? And secondly, is it possible upon the basis of this observation to explain the origin of aberrant gastric ectopia at the umbilicus without resorting to the dangerous assumptions, such as those of Tillmanns and Roser? In answer to the first question there are the following facts which are helpful: In very young embryos the intestinal tract is lined by a single layer of entodermal epithelium which is everywhere of uniform character. Later differentiation into gastric and intestinal epithelium appears and at the same time one recognizes folds and crypts which later become glands. Van Heukelom states further that the difference between stomach and intestinal epithelium occurs first at the time when the meconium or better when bile-stained material is found in the intestinal tube. Then for the first time one can differentiate the tall, regular epithelium from the intestinal epithelium, which is granular, low, shows a different kind of nuclei and contains many goblet cells. If we now remember that the portion of mucous membrane constricted off from Meckel's diverticulum was not in connection with the cavity of the diverticulum and therefore not in contact with the contents of the intestinal tract and that this separated portion of mucous membrane corresponded in histological structure to that of the stomach, the thought arises that this differentiation in the types of mucous membrane is brought about by the influence of the intestinal contents. It was van Heukelom's opinion that it is the influence of the bile which causes the differentiation into intestinal epithelium, and that the gastric mucosa and also this portion of mucosa separated from the diverticulum of Meckel, which do not come into contact with it, take on a different course of histological evolution. This explanation of van Heukelom can at once be considered as quite erroneous, for in the first place it is well known that the fetus swallows certain materials which must contain intestinal contents and therefore bile. Van Heukelom assumes, however, that this swallowed portion is without the agent, which he feels acts upon the intestine differently than upon the stomach. In the second place, in my own case, the area of gastric mucosa occupied the distal third or fourth of Meckel's diverticulum, had a perfectly free communication with it and therefore the intestine and hence was subjected to the same influences as the intestinal mucosa. There could be no doubt about this point.

One, therefore, need not assume, as van Heukelom did, that it was the total separation from the intestinal tract which caused this peculiar development of gastric mucosa.

Now as to the second question van Heukelom asks: Can the facts thus derived give a reasonable explanation for the origin of aberrant tumors of gastric mucosa, such as Tillmanns, Roser and van Heukelom himself described? The latter felt that they could. He felt that Meckel's diverticulum might of course give origin to ectopia at the navel. The difficulty in the cases of Tillmanns, Roser and van Heukelom lay in the fact that, whereas previous observers had derived the intestinal epithelium from Lieberkühn's crypts, in the latter three cases the epithelium showed the character of pylorus. Van Heukelom explains this variation by assuming that the ectopia at the umbilicus originated from the intestinal tract, inasmuch as in his own case the gastric mucous membrane was still attached to Meckel's diverticulum, which, as everyone grants, arises from intestine. The reason, then, for the variations in the initial differentiation into gastric and intestinal types of mucous membrane he explains by assuming that if the mucous membrane preserved its communication with the intestinal tract up to and beyond the period of bile formation and was thus subjected to the influences of the latter, then intestinal epithelium developed; if, however, this aberrant epithelium became separated off from the intestinal tract before the secretion of bile appeared, it developed into gastric mucosa, and thus became morphologically identical with pyloric epithelium. Van Heukelom prefers this view to accepting the hypothesis of Tillmanns and Roser as to the origin of these tissues from gastric diverticula, which view has no anatomical basis and which *a priori* is doubtful. Here again my findings refute this view, for in my own case the gastric mucosa was developed in full connection and communication with Meckel's diverticulum and therefore in the presence of bile and its influences. Van Heukelom thus derives the intestinal ectopia at the navel from portions separated off from a true Meckel's diverticulum and as a consequence divides this umbilical ectopia into two groups: the first group which separated by constriction and became isolated very early, that is, before bile formation, and thus developed into gastric mucosa; and the second group which became separated off at a later time. The former will thus contain pseudo-pyloric epithelium and later secrete an acid juice, the latter will show Lieberkühn's crypts with goblet cells and secrete an alkaline fluid.

The third explanation for the origin of this aberrant tissue is that of Salzer (1904) and Kirmisson. According to this view, the following assumption is made: At the time of the closure of the abdominal cavity, for some reason or other, there is a partial or complete cessation in evolution of the vitelline duct. As a result, the endoderm at the umbilicus is stimulated to manifold differentiation and, consequently, at one time we find a diverticulum of intestinal epithelium and at another time of gastric epithelium, and then again we may have the formation of parotid gland or pancreatic tissue. These pathological formations, according to Salzer, are always to be found at the distal end of the vitelline duct, at that point particularly

where the predisposing cause of the incomplete involution of the vitelline duct seems to be located. This cause may be in part local irritation or inflammation. In favor of the irritation or inflammatory view, these men pointed to the presence of lymphocytes, mast-cells and eosinophile cells in the mucosa. One need merely state, however, in refutation of this assumption that the finding of such cells is very common in the normal mucosa of the stomach and intestinal tract. There is the statement further that aberrant tissues are always to be found at the distal end of the vitelline duct, never at the proximal. With this assumption it would not be possible in my own case to explain the occurrence of gastric mucosa in Meckel's diverticulum, in a position certainly not subjected to irritative influences such as are supposed to be present at the umbilicus.

The fourth theory was that advanced by Albrecht and Fischl. According to this view these aberrant tissues arose from fetal inclusions or rests occurring at the time of the closure of the abdominal wall. This view is similar to that offered for the explanation of the occurrence of atypical tissues in various parts of the body. The misplaced rests from the junction points of the blastodermic layers are assumed to be the points of origin of these new tissues. It is thus assumed that these misplaced cells may retain their original powers of differentiation. This is the old teratological view for the origin of tumors and aberrant new growths. Here again one need not assume this view, for, in van Heukelom's case in the fetus and in my own, the aberrant tissue was found in the former attached to Meckel's and in the latter within Meckel's diverticulum, and thus probably was not the result of misplaced tissues at the umbilicus. In fact, in my own case the gastric mucosa was in direct continuity with the intestinal mucosa of the diverticulum. Salzer, however, admitted that in many cases in the closure of the umbilical ring there was a complete or partial persistence of the omphalomesenteric duct. Fischl felt that his theory explained more satisfactorily the fact that the abnormal formations of gastric, duodenal and pancreatic tissues are most often to be found in the distal extremity of the diverticulum than did those of Tillmanns and Salzer.

The fifth explanation offered by Lexer (1899) and Denucé (1908), whose view is doubtless most nearly the correct one, assumes that these umbilical abnormalities represent the remains of the omphalomesenteric or vitelline duct. Lexer gives no real explanation for his peculiar finding of pseudo-pyloric glands in the case of the umbilical fistula which was attached to but did not communicate with Meckel's diverticulum; but he leans toward the views of van Heukelom, that these tissues represent rests of Meckel's diverticulum rather than of gastric diverticula even in those cases in which we find a mucous membrane with gastric structure and secretion, and in which there is no anatomical connection between the umbilicus and Meckel's diverticulum. He would like to see a specimen in which there is a connection between the umbilical gastric mucosa and Meckel's diverticulum in order to afford anatomical proof for his belief. Such a case is that described by Denucé, in which case the fistula at the umbilicus did not

communicate with but was attached to Meckel's diverticulum. My own case completes the evidence, for in this case gastric mucosa is found at the tip of Meckel's diverticulum. Denucé, in spite of this latter view, cites the following facts: Originally the intestinal tract is lined throughout by a simple uniform entoderm. The differentiation into gastric and intestinal types is a later development. The cause of this differentiation in the epithelium is not clear. He suggests that isolation and occlusion of segments of a diverticulum from the intestinal tract are essential to the formation of gastric epithelium, and that there might be very early displacement in the original vitelline duct which gives rise to variations in subsequent differentiation. He is inclined to agree with van Heukelom that the occlusion of the segment is the initial cause for this variable differentiation, but he does not accept van Heukelom's view that the differentiation depends at all upon the action of the bile. He says this leads us into the domain of pure hypothesis. In other words, Denucé and Lexer lean to the view that these tissues arise from remains of the omphalomesenteric duct, namely, the intestinal tract, but offer no further explanation for the variations in subsequent differentiation. Denucé thinks that while occlusion and separation are probably responsible, the action of bile is not a factor. He gives no further explanation. Here again this view can be answered in a word, namely, that occlusion and separation are not necessary, for they surely were not present and could not be responsible for the variation in my own case.

In a review of the cases reported in the literature of aberrant glandular tissue occurring in Meckel's diverticulum itself, I have been unable to find mention of the occurrence of gastric mucosa. In the search it became apparent, however, how often, relatively, pancreatic tissue has been found in the intestinal tract; in fact, cases were found in which pancreatic nodules occurred in the stomach, duodenum, jejunum, ileum and even in Meckel's diverticulum. There were no cases found in which pancreas was discovered below Meckel's diverticulum, a fact which will be considered again. Because of the relative frequency with which aberrant pancreas has been found in the intestinal tract, a brief review is given of these cases and finally a few others are also reported in which Lieberkühn's and Brunner's glands and pancreatic tissue were found in Meckel's diverticulum. There is one case also reported in which pancreas was found at the umbilicus. These cases are reviewed with the hope that they may throw some light upon our own case and in general upon the occurrence of gastric mucosa at the umbilicus and in Meckel's diverticulum. The case reports are reviewed in groups according to the location of the aberrant pancreatic tissue; the first cases being those in which pancreatic tissue occurred in the stomach wall, then in the duodenum, jejunum, ileum, Meckel's diverticulum and at the umbilicus. In only a few instances are the histological descriptions complete and in many instances not really convincing enough to make one feel that the author was really dealing with true pancreatic tissue. On the whole, the explanations offered for these abnormal findings are rather unsatisfactory. Reference, however, will be made to them in order to

complete our review of the theories which have been offered to explain these occurrences.

Klob¹¹ (1859) found a flat, circular swelling, of glandular appearance, inserted between the peritoneal and muscle coats, in the middle of the greater curvature of the stomach. Upon microscopic examination this glandular mass showed pancreatic structure throughout. No further description or measurements are given. Klob called this tissue "*pancreas accessorium*." In substantiation of the belief that he was dealing with an accessory pancreas, he refers to Leydig,¹² who claims that in the land salamander in the wall of the jejunum and in pelobates in the wall of the stomach one can find isolated portions of the pancreas with excretory ducts.

Gegenbauer¹³ (1863) similarly described an accessory pancreas occurring in the wall of the stomach, 2 cm. from the pyloric sphincter and near the lesser curvature. It consisted of a rounded, somewhat elevated, tumor mass 14 mm. in width and 6 mm. in thickness and covered everywhere by stomach mucous membrane. Upon microscopic examination the mass was found to be an acinous gland, resembling pancreas in structure. No further description is given. He found a small duct opening upon the surface.

Merkel¹⁴ (1905) described two cases of pancreatic rests occurring in the submucosa of the stomach.

Wagner¹⁵ (1862) described two cases of aberrant tissue occurring elsewhere than in the normal location. In one of these cases, which was very similar to Gegenbauer's case described above, the pancreatic tissue occurred in the wall of the stomach.

Hyrtl¹⁶ (1860) mentions a rare occurrence of accessory pancreatic tissue behind the arteria and vena mesenterica superior and surrounding these vessels at their roots.

Bernard¹⁷ (1858) described a second, smaller, pancreatic duct communicating with the main duct, oftentimes, however, emptying independently just below the main duct, in man, dog, cat and rabbit. Bernard has also described tubulo-acinous glands in the wall of the duodenum, which are supposed to have the same physiological properties as the pancreas.

Klob¹⁸ (1859), in a second case similar to the one he described above, found a mass in the posterior wall of the first portion of the jejunum, 4 cm. beyond the duodeno-jejunal turn. No duct was found. Upon microscopic examination the mass was found to consist of pancreatic tissue.

Merkel¹⁹ (1905) described a pancreatic rest in the subserosa of the jejunum.

Zenker²⁰ (1861) described a frequent variation called the "*pancreas minus*," a lobe of pancreatic tissue possessing a kind of attachment to the caput pancreatis and emptying usually into the *ductus wirsungianus*, often, however, 1 cm.-1.5 cm. below the normal duct. Zenker records five cases, in three of which the accessory pancreas occurred in the wall of the small intestine. In the fourth case there were two accessory pancreases, one 16 cm. the other 48 cm. below the duodenum. The most curious was the fifth case: in this one there occurred, 54 cm. above the cecal valve, a finger-like, true diverticulum 5.5 cm. long, with a narrow, fatty mesentery, in the fat

of which the accessory pancreas was found situated near the tip of the diverticulum. In a foot-note Zenker says:

Vielleicht bezieht sich eine alte von Meckel (Patholog. Anat. I Bd. S., 590) citirte Beobachtung von Schulze auf einen gleichen Fall. Dieser (Acta. natur. curios. Tom. T. Obs. 226, p. 504, Ao. 1727) fand bei einem Neugeborenen an der Spitze eines wahren Darmdivertikels "eine drüsenähnliche Warze." (Im original heisst es, culus apicem glandulosa papilla quaedam quasi coronabat.) Da dieselbe nicht weiter beschrieben ist, lässt sich freilich darüber nicht entscheiden. Vielleicht ist damit auch nur eine jener Ausstülpungen gemeint, die sich bisweilen an der Spitze des Divertikels finden.

The location of the accessory pancreas in the bowel wall varies. It may be in the submucosa or between the serosa and muscularis. Zenker gives a general histological description, makes no mention of the zymogen granules or islands of Langerhans and states simply that the general structure was that of true pancreas. He was able to find a duct in all his cases. The largest accessory pancreas of this series had a diameter of 3.5 cm. The true pancreas in all cases was normal. He regards the occurrence of accessory pancreas as a developmental anomaly originating in the earliest anlage of the pancreas.

Zenker thinks these anomalies can be explained as follows: The usual pancreatic evagination is single, sometimes double, occasionally triple for the first anlage. These evaginations when multiple then develop into separate glandular bodies. In the further course of development, one becomes the main, true pancreas; the remaining evagination, either above or below the pancreatic duct, is carried upwards or downwards by the further growth and elongation of the original straight intestine. If above, it comes to lie in the wall of the stomach; if below, it may occur either in the duodenum, jejunum, small intestine or even in Meckel's diverticulum. The last would be the lowest possibility, as Meckel's diverticulum lies at the transition line between the upper and the lower intestine. It is difficult to understand how the gastric anlage in our case could get below the embryologically possible position of the pancreas or how gastric mucosa normally above could get below the level of the pancreatic duct according to this explanation. Zenker could find no evidence of an effect of the accessory pancreas upon the digestion in these individuals.

Several cases are reported further of the occurrence of pancreatic rests in Meckel's diverticulum. Thus Merkel (1905) demonstrated a pancreatic rest or anlage in the tip of Meckel's diverticulum.

Neumann²² (1870) found, in a child 10 months of age, a swelling the size of a small bean attached to the tip of Meckel's diverticulum by a short pedicle. In its center was a lumen connected by a kind of duct with the lumen of the diverticulum. Upon histological examination, this body was said by Neumann to have gland alveoli resembling in appearance those of the pancreas. No further description is given. This case in many respects resembles the one of the human fetus reported by van Heukelom, except that in this instance the nodule was completely constricted off from Meckel's diverticulum at its tip, separated entirely from the lumen and was

composed of gastric mucosa. It is interesting to have two cases in many respects simulating one another, one case composed of pancreatic tissue, the other of gastric tissue.

Regarding this anomaly as a Meckel's diverticulum, and this in turn as coming from the ductus omphalomesentericus, Neumann finds it difficult to see an association between the presence of the diverticulum and the occurrence of pancreas. Neumann suggests that the former may not have been a true Meckel's diverticulum, but rather a secondary formation due to mechanical pull of the evaginating glandular mass on the bowel wall. The location of the diverticulum and the subsequent report of a number of similar findings in true Meckel's diverticula would indicate that this evagination was probably also a true Meckel's diverticulum.

A good description, together with illustrations of a case in which an accessory pancreas was found at the tip of a Meckel's diverticulum, was given by Bize²³ in 1904.

Albrecht²⁴ (1901) found in the tip of Meckel's diverticulum a yellowish nodule, about the size of a pea, which resembled microscopically typical pancreatic tissue. In this case, contrary to many other cases described, the author takes pains really to identify the new tissue formation. He mentions the occurrence of abundant zymogen granules in the cells, centro-acinous cells, islands of Langerhans, ducts emptying into the lumen of the intestine, nerves and blood-vessels occurring in normal fashion. Five, possibly six, cases of similar nature are reported in the literature, but without further discussion or description.

In regard to the origin and development of these structures this author suggests that they are possibly:

1. *Aberrant Pancreas*.—He thinks this possibility cannot be denied, for on the basis of comparative anatomy it has been shown by v. Kupffer that in the sturgeon pancreatic tissue has been found in the ductus choledochus. Others have demonstrated the occurrence of pancreas in the papilla minor. These probably represent isolated portions of the original anlage. It is questionable, however, according to this author, whether such rests would be found as low down as the umbilicus. Furthermore, this conception does not explain why these rests, when found in the region of the lower ileum, occur regularly in the tip of Meckel's diverticulum.

2. *Rests of Glandular Formations Originating from the Yolk Stalk or Sac*.—That such an origin might be possible is perhaps indicated by the findings of Graf Spee, who described in the yolk sac in the case of the human embryo numerous tubular glands with prismatic epithelium. Opposed to this view, however, is the fact that an analogy of the normal pancreas is impossible, and furthermore that one would have to imagine that a complete metaplasia of an embryonic organ had taken place.

3. *The Atavistic Formation*.—There is no evidence for this view.

4. *"Carapogenetic"*.—By exclusion, this conception seems to be more probable as compared with those just mentioned. Whichever view one prefers, a number of interesting thoughts arise. In the first place, the same general developmental fac-

tors or influences must have been present which determined the formation of the normal pancreas, except for the causes of the greater growth and the topographical relationship of the normal pancreas. Thus at once we are forced to dismiss the belief that pancreas develops as a result of factors which are present only in the region of the duodenum, such as certain mechanical combinations or strictly localized hormones or similar tissue-stimulating substances. It would seem that, according to this author, the influences which can give rise to these aberrant pancreatic formations are not specific for the duodenum. In fact, the specific reasons for the occurrence of this aberrant pancreas must be sought for in the potentiality for pancreatic formation in the whole small intestinal portion of the original intestinal anlage, namely, the entoderm, certainly in that portion extending from the normal pancreas anlage down to the ductus omphalomesentericus. Perhaps the frequent location of the heterotopic pancreas in the tip of Meckel's diverticulum is consequent upon causative factors similar to those responsible for the formation of pancreas in both instances and sharply localized in the immediately contiguous bowel. These factors may be of a mechanical character.

In conclusion this author speculates upon the possible benefit this type of pancreas can have for its possessor. Since, at least in this present instance, the aberrant pancreas was capable of active normal secretion, it would seem to all appearances that there was a lessening of the danger to the patient of stagnation of the intestinal contents with its consequent possible mechanical and infectious complications, Meckel's diverticulum in this instance being 25 cm. long.

Brunner,⁴ as cited by Tschiknawerow, found in a case of invagination, in a child four and a half years old, a Meckel's diverticulum, 37 cm. above the ileocecal valve, which had at its blind tip a tumor measuring, in its various dimensions, 25 x 22 x 19 mm. Microscopic examination of the tumor showed it to be composed of two parts: one consisting of adipose tissue; the other composed of gland lobules, ducts and lymphoid nodules and resembling pancreas in structure.

Hedinger¹¹ (1906) demonstrated in the body of a 30-year-old man, dead of cardiac disease, a Meckel's diverticulum 5 cm. in length. In the wall at the tip of the diverticulum a granular, light yellow nodule of tissue was found measuring 2.5 cm. in length and .5 cm. in width. Microscopical examination showed this nodule to consist of typical pancreatic tissue with an occasional duct and with a second lobule resembling Brunner's glands in structure. He adds a review of the literature bearing upon similar findings and discusses the significance of them.

Nazari¹² (1909) reports the occurrence of aberrant pancreas in the tip of Meckel's diverticulum.

Tschiknawerow¹³ described three cases of Meckel's diverticulum in which pathological tissue formation was found.

In Case I he described a spindle-celled sarcoma occurring in the diverticulum.

Case II was that of a man 25 years of age who had died of pneumonia. At the tip of and extending into the lumen of the diverticulum, which was 3 cm. long, there was found a small

body, 1 cm. in length. Near the surface of this enlargement glands of the Lieberkühn type were found, while those in the depths resembled Brunner's glands both as to structure and as to position. The remaining mucosa of the diverticulum had the structure of intestine. The villi were well marked, lymph follicles occurred in areas, and everywhere typical Lieberkühn's glands were present.

Case III was that of a woman of 55 years of age. At the tip of Meckel's diverticulum, which measured 7 cm. in length, there occurred a rather hard swelling which was found to consist of atypical Lieberkühn's glands and to resemble pancreas to a certain extent.

Lecène¹⁴ described an adenoma developing at the level of the free end of a Meckel's diverticulum.

A number of additional instances are reported of aberrant pancreas occurring in intestinal diverticula other than in the true diverticulum of Meckel. The aberrant tissue in the bowel wall is supposed by many to be the primary factor in the subsequent formation of these diverticula, which then enlarge by a secondary evagination of the bowel wall due to pressure within its lumen at a point probably weakened by the glandular mass. Whether this conception is correct or not remains an open question.

Nauwerk¹⁵ (1893) reports the occurrence of a diverticulum 9 cm. in length, occurring 2-3 mm. above the ileocecal valve in which an accessory pancreas was found, covered on the outside by serosa and having an excretory duct. He explains the formation of the diverticulum by the mechanical pull of the accessory pancreas on the bowel wall. In addition to pancreatic acini a hyperplastic overgrowth of Lieberkühn's glands was also found, and the impression was gained that numerous transitions occurred between these overgrown Lieberkühn's glands and the true pancreatic lobules. Besides this diverticulum a true Meckel's diverticulum was also found, measuring 3 cm. in length and situated 80 cm. above the ileocecal valve.

Further examples of this condition are reported by Thompson,¹⁶ Hulst¹⁷ and Albrecht and Arzt.¹⁸

A case of pancreas occurring at the umbilicus was described by Wright.¹⁹ In a girl 12 years of age there was found a congenital umbilical fistula which, after breaking down twice following operation, healed as a result of complete extirpation of the fistulous tract in which a pancreas nodule was found.

Franckh²⁰ (1893) has described in greater detail the anomalies which are apt to occur in the remains of the vitelline canal.

DISCUSSION

It is seen, then, that the occurrence of aberrant glandular tissue, particularly gastric and pancreatic, may occur in the stomach, intestine, Meckel's diverticulum, in the obliterated cord connecting the latter with the umbilicus and at the umbilicus itself. These aberrant tissues have a great interest for embryologists in view of their possible explanation and to pathologists for this reason also, and furthermore for the reason that new growths and other pathological processes may arise from these aberrant tissues. To the surgeon, furthermore,

because they may be the seat of inflammation, perforation, abscess formation and even subsequently of intestinal obstruction. In general, very few complete histological studies with the idea of absolutely determining the nature of these tissues under consideration have been reported. As a consequence, there has been considerable confusion in the past in certain instances as to the exact type of glandular tissue with which one was dealing. The case reported in this present publication offered, therefore, a good opportunity for positively identifying in the tip of Meckel's diverticulum an area of gastric mucosa of the fundus type. This was done beyond question, and therefore the facts can be used in clearing up or in refuting a number of theories which have been offered in the past to explain the origin of these aberrant tissues and to furnish certain facts for a more probable theory as to their origin.

Speaking in the first place of aberrant mucosa it may be recalled that several cases of gastric mucosa occurring at the umbilicus, in the form of polyps, depressions or fistulae, were reported by Tillmanns, Reichard, Roser, Weber, Lexer, Denucé and a few others. In one or two instances such a fistula was blind and was attached at its inner extremity to a fibrous cord or to Meckel's diverticulum itself. The latter in these instances had the structure of intestinal epithelium. In one instance, namely, that of van Heukelom, there was found in a human fetus a small nodule of gastric mucosa at the tip of Meckel's diverticulum which had become completely constricted off and separated from the lumen of the diverticulum, but was still attached to the latter.

In many of these cases the reports, in which histological examination was more or less incomplete or not made at all, are rather unsatisfactory. In only one instance, I may say, was there a very careful histological examination made, namely, by Denucé, who reported mucosa of the gastric fundus type occurring at the umbilicus. Aside from this there were no other cases in which gastric fundus mucosa was found or described. My own case, then, represents the only one in the literature in which a considerable area of mucosa at the tip of Meckel's diverticulum, communicating freely with it and in continuity with the remaining mucosa of the diverticulum, was found to be of the gastric fundus type or even gastric at all.

In this manner, then, the link in the chain of evidence which goes to show that this aberrant gastric tissue arises from remnants of the omphalomesenteric duct is complete.

Several of the theories which have been advanced to explain the origin of this tissue are thus effectively answered in the negative. Thus, Tillmanns' theory, which had few adherents and which supposed that gastric mucosa occurring at the umbilicus is derived from gastric diverticula, becomes quite improbable. Van Heukelom had already quite effectively answered this theory.

The second theory is that of Siegenbeck van Heukelom, who believes that these aberrant growths at the umbilicus and at the tip of Meckel's diverticulum represent the remains of the vitelline duct. He, however, felt that the differentiation into gastric or intestinal epithelium depended upon whether or

not the mucosa in early fetal life had become differentiated before or after the influence of bile had become effective. This view is doubtless in part correct, but not altogether, for again my findings show that gastric mucosa may differentiate from the intestinal epithelium even under the same influences so far as concerns the action of the intestinal contents. In other words, isolation of the mucosa very early in fetal life is not essential for the development of gastric mucosa.

The third explanation, namely, that of Salzer, that misplaced entoderm at the umbilicus is stimulated to a variable differentiation by irritation or inflammation and consequently may give rise to gastric, intestinal, or even pancreatic tissue, similarly does not fully explain, for again, as my case shows, gastric mucosa may develop in the absence of such irritative or inflammatory conditions.

The fourth theory, that of Albrecht and Fischl, that these aberrant tissues arise from fetal inclusions or rests occurring at the umbilicus at the time of the closure of the abdominal wall, similarly does not suffice, for the occurrence of these tissues in the tip of Meckel's diverticulum can certainly occur without these factors being present.

The fifth explanation, which is doubtless the most nearly correct, was practically accepted by Lexer and by Denucé. These authors assumed that these umbilical abnormalities represent the remains of the omphalomesenteric or vitelline duct, although no very detailed facts have been offered to support this view. My own case would complete the evidence so far as gastric mucosa is concerned, for it shows in the first place that gastric mucosa can and does arise from the remains of the vitelline duct if one assumes, which is doubtless correct, that Meckel's diverticulum itself is the representative of such remains. One need assume no further factors nor circumstances, such as improbable constrictions in the stomach or misplacements and irritations affecting the entoderm, which are thus caused to undergo this peculiar differentiation. It becomes evident then how important this finding has been, because it has allowed us to answer effectively the previous views and to furnish indisputable evidence that the gastric mucosa as reported in previous cases occurring at the umbilicus has doubtless arisen from the omphalomesenteric duct. As to the ultimate influences which have caused this differentiation one cannot state definitely in the present condition of our knowledge concerning these processes.

The sixth and last explanation, practically that of Albrecht, is, so far as present evidence goes, the most nearly correct, and this holds for pancreatic tissue or gastric or in fact any of the glandular tissues of the intestinal tract, such as Brunner's glands. According to this view the original entodermal lining of the intestinal tube and omphalomesenteric duct possesses potentialities of development into any of the glandular structures in the adult intestine or of its accessory glands, and under the influence of certain circumstances, which we do not understand, groups of cells may retain one or the other potentiality and develop into a glandular tissue or organ very different from the surrounding glandular tissue and resem-

bling the adult organ, such as stomach or pancreas, which may be far removed.

In view of his findings of aberrant pancreatic tissue at various points in the intestinal tract, Zenker felt that these anomalies represented pancreatic anlagen, which in the further course of development were carried upwards or downwards by the further growth and elongation of the original straight intestine and which might come to lie hence in the stomach or in any part of the intestinal tract down to and including Meckel's diverticulum. If this assumption is made in the case of the pancreas, then one should assume the same, I think, in the case of the stomach, in which instance it seems quite impossible to believe that a gastric anlage could by such mechanism become displaced so far as to lie below the possible embryological position of the pancreas. One certainly could not apply this view to the occurrence of gastric mucosa at the umbilicus or in Meckel's diverticulum.

Finally, Albrecht's view as stated above is probably the correct one. If we accept this view of the uniform potentiality of the entoderm to develop into any of these glandular tissues, we can readily understand how cases of aberrant stomach, pancreas, Lieberkühn's glands and Brunner's glands can occur anywhere in the intestinal tract as far down as Meckel's diverticulum. The intestine below Meckel's diverticulum which represents the hindgut doubtless has not these potentialities, as a consequence of which these aberrant structures have never been found below the level of Meckel's diverticulum.

To summarize then, I have reported a case of a young man, 19 years of age, who presented before operation symptoms and signs suggestive either of acute appendicitis or partial intestinal obstruction. On examination, among other things there was found just below the umbilicus a scar which had been produced by a former operation for an abscess. The nature of the abscess was not determinable. Upon subsequent operation it was found that the small bowel had become strangulated over a thick, fleshy cord consisting of Meckel's diverticulum and some adherent omentum which fastened the former to a point on the anterior abdominal wall just below the umbilicus. Excision of Meckel's diverticulum with the adherent omentum was done and the patient made an uneventful recovery.

Upon examination of the open diverticulum there was found in the distal third or fourth of the diverticulum an area of thickened, irregular, granular, dark red mucosa which was demarcated sharply from the proximal pale finer mucosa, which in turn was of intestinal character. Furthermore, upon careful histological examination this distal segment was found to consist of a mucosa definitely resembling in every particular that of the gastric fundus region. The glands were precisely of the fundus type and showed the characteristic zymogen granules of the chief cells and the eosinophilic granules of the parietal cells as characteristic in the glands of the stomach.

Upon a careful search of the literature it is found that a number of cases have been reported of the occurrence of gastric mucosa at the umbilicus in the form of polyps or fistulae.

Other aberrant tissues, such as pancreas, have been described along the intestinal tract and even in one instance in a nodule at the tip of Meckel's diverticulum and connected with its lumen. Another interesting case reported is that of van Heukelom in which a nodule of mucosa was found at the tip of Meckel's diverticulum, constricted off from it, not connected with the lumen, but attached by a fibrous cord. This mucosa proved to be of pyloric nature. My own case is the only one of which I am aware of gastric mucosa occurring in the wall of Meckel's diverticulum and in free communication with its lumen. Careful histological examination was made necessary because of the rather uncertain findings reported by previous authors and of the various theories which have been constructed to explain the occurrence of these aberrant tissues at the umbilicus.

The finding in my own case of gastric mucosa in Meckel's diverticulum, which it is agreed quite generally is a definite remains or persistence of the vitelline or omphalomesenteric duct, makes it appear certain that these aberrant tissues occurring at the umbilicus, in fibrous cords and in Meckel's diverticulum, have a uniform origin, namely, from the entoderm of the original intestinal tube or yolk stalk. It was very important to complete the evidence that these aberrant tissues may arise anywhere along the tract of the original omphalomesenteric duct in order to answer the various hypotheses which were previously advanced.

After a review of these hypotheses and in view of the evidence that I have brought forward, the best explanation for the occurrence of these structures is, that the original entodermal lining of the intestinal tube and omphalomesenteric duct possesses potentialities of development into any of the glandular structures of the adult intestinal tract or of its accessory glands, and under the influence of certain circumstances, which we do not understand, groups of cells may retain one or the other potentiality and develop into a glandular tissue very different from the surrounding glandular tissues and resembling the adult organ, such as stomach or pancreas, which may be far removed. The finding in my case of gastric mucosa in Meckel's diverticulum effectively answers the various theories that the gastric growths at the umbilicus may have arisen by constriction or separation from gastric diverticula in the early fetus, or that a differentiation in the mucosa or in these aberrant tissues is brought about by the presence or non-presence of the bile, or that irritations, inflammations or fetal inclusions at the point of union of the blastodermic layers are necessary. In fact, there is good evidence now, with the findings in my own case, for believing that these aberrant tissues arise from remains of the omphalomesenteric duct; but as to the ultimate factors which cause this differentiation we cannot state in the present condition of our knowledge.

The finding of this gastric mucosa explains well the reasons for the finding of acid secretion with digestion at the umbilicus, in cases of umbilical polyps and fistula as reported in the literature, although cases in which gastric mucosa oc-

curred at the umbilicus had been reported before. Again, we have a good embryological basis for understanding certain adenomatous tumors and growths of an intestinal glandular nature occurring at the umbilicus, in obliterated intra-abdominal umbilical cords and in Meckel's diverticulum. In fact, in the case reported it is interesting to speculate as to the condition for which the patient had been operated upon several years previously. It seems probable that there was at that time a perforation at the tip of Meckel's diverticulum, though none was found at the operation. As a consequence of this an abdominal abscess formed which was simply drained and which healed with the formation of adhesions between the tip of Meckel's diverticulum and the anterior abdominal wall. It is interesting to think also that this perforation at the tip of Meckel's diverticulum might well have been a perforative gastric ulcer, for so far as the structure of the mucosa went we were certainly dealing with the fundus type of mucous membrane. This perforation evidently healed subsequently. The case further illustrates the desirability of examining carefully all cases of Meckel's diverticulum for the possibility of occurrence of aberrant glandular tissues in the mucosa, both for embryological reasons and also because of the importance of these structures in pathology and certain surgical conditions.

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BIBLIOGRAPHY

- Albrecht, E.: Ein Fall von Pankreasbildung in einem Meckel'schen Divertikel (Abstr.), München. med. Wehnschr., 1901, XLVIII, 2061; also, Sitzungsber. d. Gesellsch. f. Morphol. u. Physiol. in München (1901), 1902, XVII, 52, cited by Tschikna.
- Albrecht, H., and Arzt, L.: Beiträge zur Frage der Gewebsverfrüfung. (2) Ueber die Bildung von Darmdivertikeln mit dystopischem Pankreas. Frankf. Ztschr. f. Path., Wieb., 1910, IV, 167-186.
- Bize: Étude anatomo-clinique des pancréas accessoires situés à l'extrémité d'un diverticule intestinal. Revue d'orthop., Paris, 1904, 2^s, V, 149-159.
- Blesley, R. R.: The structure of the glands of Brunner, The Decennial Publications. The University of Chicago Press, 1903, X.
- Bernard, C.: Leçons de phys. expérim. Tome II, Schmidt's Jahrb., 1858, XCVII, 21.
- Brunner, C.: Ein Beitrag zur Chirurgie und pathologischen Anatomie der Darminvagination. Beitr. z. klin. Chir., 1895, XXV, 345.
- Cullen, T. S.: The umbilicus and its diseases. W. B. Saunders Company, Philadelphia and London, 1916.
- Denucé, M.: Fistules pseudopyloriques congénitales de l'ombilic. Revue d'orthopédie, 1908, IX, 1-29.
- Franchomme, H.: Anomalies de régression du canal vitellin; diverticule de Meckel, fistules ombilicales. 4^e, Paris, 1893.
- Gegenbauer, C.: Ein Fall von Nebenpankreas in der Magenwand. Arch. f. Anat., Physiol. u. wissensch. Med., Leipzig, 1863, 163-165.
- Hedinger: (Fall von Mekelschem Divertikel mit Pankreasgewebe und Brunnerschen Drüsen an der Spitze desselben.) Corr.-Bl. f. schweiz. Aerzte, Basel, 1906, XXXVI, 395. 1. Wintersitzung Dienstag, den 3 Okt., 1905.
- Hulst, J. P. L.: Ueber einen in einem Darmdivertikel gelagerten Pankreaskeim mit sekundärer Invagination. Centrabl. f. allg. Path. u. path. Anat., Jena, 1909, XX, 12-15.
- Hyrtl, J.: Handbuch der topographischen Anatomie und ihrer praktisch medicinisch-chirurgischen Anwendungen, 46, 1860, L, 667.
- Klob, J.: Pankreas-Anomalien. Ztschr. d. k. k. Gesellsch. d. Aerzte zu Wien, 1859, XV, 732.
- Lecène, P.: Adénome développé au niveau de l'extrémité libre d'un diverticule de Meckel. Bull. et mém. Soc. anat. de Par., 1912, LXXXVII, 63.
- Lexer, E.: Magenschleimhaut im persistirenden Dottergang. Arch. f. klin. Chir., 1899, LIX, 859-865.
- Leydig, F.: Lehrbuch der Histologie des Menschen und der Thiere, 1857, 352, cited by Zenker.
- Lindner, M. H.: Discussion: Ein Fall von Exstirpation des persistirenden Ductus omphalo-mesentericus. Deutsche med. Wehnschr., 1898, XXIV, 172v.
- Merkel: Discussion: Abgesprengte Pankreasanlagen. München. med. Wehnschr., 1905, LII, 337.
- Minelli, S.: Adenoma Ombelicale a Struttura gastrica. Gazz. med. ital., Torino, 1905, LVI, 101-105.
- Nauwerck, C.: Ein Nebenpankreas. Beitr. z. path. Anat. u. z. allg. Path., Jena, 1892, XII, 29-32.
- Nazari, A.: Pankreas aberrato in un diverticolo di Meckel. Bull. d. r. Accad. med. di Roma, 1909, XXXV, 245-250.
- Neumann, E.: Nebenpankreas und Darmdivertikel. Arch. d. Heilk., Leipzig, 1870, XI, 200.
- Reichard, V. M.: Demonstrationen zur Magen-Darmchirurgie. Zentrabl. f. Chir., 1898, XXV, 587-588.
- Roser, W.: Zur Lehre von der umbilicalen Magencysten-fistel. Zentrabl. f. Chir., 1887, XIV, 260.
- Salzer, H.: Ueber das offene Meckelsche Divertikel. Wien. klin. Wehnschr., 1904, XVII, 614-617.
- Strada, F.: Adenoma congenito ombelicale a tipo gastrico (Contributo allo studio dei tumori congeniti dell'ombelico). Sperimentale Archiv. di Biol., 1903, LVII, 637-658, 1 pl.
- Thomson, A.: Diverticula of the alimentary tract, with particular reference to those met with in the ileum resulting from an accessory pancreas and from tuberculosis. Tr. Med.-Chir. Soc. Edinburgh, 1908, n. s. XXVII, 118-129, 2 pl.
- Tillmanns, H.: Ueber angeborenen Prolaps von Magenschleimhaut durch den Nabelring (Ectopia ventriculi) und über sonstige Geschwülste und Fisteln des Nabels. Deutsche Ztschr. f. Chir., Leipzig, 1882-3, XVIII, 161-202.
- Tschikna, L.: Zur Kenntnis der pathologischen Gewebsbildungen in Meckel'schen Divertikel. Berl. klin. Wehnschr., 1911, XLVIII, 1676-1679.
- van Heukelom, S.: Die Genese der Ectopia ventriculi am Nabel. Virchow's Arch., 1888, CXI, 475.
- von Rosthorn, A.: Ein Beitrag zur Kenntnis der angeborenen Nabel-fisteln. Wien. klin. Wehnschr., 1889, II, 125; 154.
- Wagner, E.: Accessorisches Pankreas in der Magenwand. Arch. d. Heilk., Leipzig, 1862, III, 283.
- Weber, W.: Zur Kasuistik der Ectopia Ventriculi. Beiträge z. klin. Chir., 1898, XXII, 371-385.
- Wright, J. H.: Aberrant pancreas in the region of the umbilicus. J. Boston Soc. Med. Sc., 1900-1, V, 497-498, 1 pl.
- Zenker, F. A.: Nebenpankreas in der Darmwand. Arch. f. path. Anat. (etc.), Berlin, 1861, XXI, 369-376.

end representing 0° and the left-hand end 180° . At the center of this line is placed the point H representing the heart, the electrical axis of which is diagrammatically illustrated by the arrow $p-q$. Rotation, then, counter-clockwise of the axis above this horizontal line represents a negative angle, whereas rotation clockwise below the horizontal represents a positive angle. The normal electrical axis is illustrated by the direction of the arrow in the figure in which the angle α , the angle of deflection between the arrow $p-q$ and the horizontal line corresponding to the plane of Lead I, measures in our figure $+55^\circ$.

If upon this arrow indicating the direction of the axial current we mark off two points p and q , Einthoven has shown that the distance between lines projected from these points at right angles to any one of the three sides of the triangle, which correspond to the three leads, will represent the amplitude of the deflections for that lead, and that under all normal conditions the amplitude of $R_1 + R_2 = R_3$. Furthermore, from the amplitude of these deflections we may determine the direction of the axis of potential difference in the heart and may calculate the angle α , thus determining in degrees the rotation of the electrical axis in the sagittal plane and the accurate measurement of the angle formed in relation with the horizontal plane representing Lead I (R. A.-L. A.).

It should be clearly understood that the amplitude of any given deflection represents the difference in potential in the electrical axis existing in the heart at a given instant of time in relation to the lead employed, and that this amplitude will vary as the electrical axis alters its position in relation to this lead. Hence, it is evident that the amplitude of any given deflection may not represent the greatest difference of potential possible in that lead, and Einthoven insists that we must distinguish between what we may call the recorded difference of potential and the maximal possible deflection, which he designates as the "manifest potential difference" or the "manifest value."

This manifest value depends upon the maximal distance separating the two points between which the potential difference is developed and is only met with when the electrical axis and the lead employed lie in parallel planes. It can be calculated from the height of the recorded curves and can be expressed in absolute measure in millivolts by multiplying the deflection measured in millimeters by 10^{-4} when the galvanometer string has been standardized for the usual deflection. In determining the angle α , however, for all clinical purposes we may disregard this manifest value, though a table giving the various determinations of this potential difference is incorporated in the last paper referred to above.

Einthoven's formulæ are as follows: If we let $p-q=E$, representing the manifest value, $p_1 - q_1 = e_1$, $p_2 - q_2 = e_2$, $p_3 - q_3 = e_3$, then

$$e_1 = E \cos \alpha. \quad (1)$$

$$e_2 = E \cos (\alpha - 60). \quad (2)$$

$$e_3 = E \cos (120 - \alpha). \quad (3)$$

$$e_3 = e_2 - e_1. \quad (4)$$

It is evident that under these conditions the potential difference present between the angles of the triangle must bear the following relationship $e_1 : e_2 : e_3$. From these data when the angle α is unknown it can be determined from the relationship of any two of these potential differences from the following formulæ:

$$\text{Using } e_1 \text{ and } e_2 \text{ tg. } \alpha = \frac{e_2 - e_1}{e_1 \sqrt{3}}. \quad (5)$$

$$\text{Using } e_1 \text{ and } e_3 \text{ tg. } \alpha = \frac{e_3 + e_1}{e_1 \sqrt{3}}. \quad (6)$$

$$\text{Using } e_2 \text{ and } e_3 \text{ tg. } \alpha = \frac{e_2 + e_3}{(e_2 - e_3) \sqrt{3}}. \quad (7)$$

We have stated above that under normal conditions this law that $e_3 = e_1 + e_2$ holds true. That clinically, however, we constantly meet with apparent exceptions to this statement is a matter of common observation. It must be kept in mind that while we are dealing theoretically with a flat plane we have actually to do with a very complicated muscle mass and it is the more remarkable that this seeming exception to this fundamental law is apparent rather than real, and that it is due, as Einthoven has shown, to the phasic variation between similar peaks of the electrocardiogram.

In order to determine exactly the proportional amplitude of a given deflection in the three leads, especially in all instances showing conspicuous phasic variation, we must know the exact time relationship of the deflection to the cardiac cycle in each of the three leads. Manifestly, this can only be determined by simultaneous records of the heart sounds and the electrocardiogram, such as have been made by Fahr,* or by the use of two galvanometers as employed by Williams.* Fortunately, this apparent exception to the simplicity of the fundamental principle involved does not invalidate the application of the formulæ given above in all normal instances and may be corrected for as Einthoven has shown in the more obscure forms.

Using two galvanometers Williams (*l. c.*) has shown by the projection of vectors determined from the manifest value e , in conformity with the different leads, the essential nature of this phasic variation in homonymous peaks of the electrocardiogram, and has further demonstrated that the bizarre curves met with are due entirely to the manner in which the direction of potential difference is shifting within the heart, and that, although the peaks are absolutely in phase in only a few instances, such absolute accuracy in the calculated values is not essential for the majority of clinical records.

Based upon the principle of the equilateral triangle Pardee* has published a graphic method by which the negativity of the initial ventricular deflections determines within the limits of 60° the direction of the axis of potential difference. This is accomplished by dividing the circumference of the circle into six quadrants, into any one of which it can be shown, by the positivity or negativity of the recorded deflections, that the axis of potential difference must fall.

It is interesting to note how closely the angle, determined by means of the tables published by Einthoven, Fahr and De Waart, coincides with the results calculated by the use of

their formulæ 5, 6 and 7 given above. These observers have further demonstrated that the angle varies with inspiration and expiration in different individuals from 12° to 36° , being always greater in inspiration than in expiration, the normal angle falling between $+40^\circ$ and $+90^\circ$.

In a true left ventricular preponderance the angle α has a value approaching -20° , falling between 0° and -40° , while with a right ventricular preponderance it has a value approximating $+120^\circ$, falling between $+90^\circ$ and $+150^\circ$. If we assume that the electrical axis in these cases originally had a normal value, we must postulate a rotation of the direction of potential difference through an arc of from 70° to 140° . That this, however, implies a rotation of the anatomical axis of the heart throughout anything like the same extent is manifestly absurd, and the explanation for the rotation of the axis of potential difference must be sought in the shifting balance of the muscle mass and the ensuing relationship of the plane of the electrical axis to the Derivations I and III.

Figs. 2, 3 and 4 may serve to make this point clear. Fig. 2 illustrates the normal direction of the axis of potential difference. In this figure the excitation wave passes from base to apex within the heart and from apex to basal structures through the galvanometer, the deflections being upright in all three leads. In Fig. 3, the deflections are upright in Leads I and II, though the predominant deflection may be downward in Lead II, and downward in Lead III; while in Fig. 4, the deflections are downward in Lead I, and upright in Leads II and III. The direction of the course of the difference in potential is indicated in each instance by the direction of the arrow.

In a paper upon the localization of the origin of the excitation wave in the human heart, Fahr and Weber⁷ have demonstrated the soundness of the principle involved in the use of the geometric figure and the facility with which one can graphically determine the measurement of the angle α and the direction of the axis of potential difference by plotting upon an angle of 60° the values, in tenths of a millivolt, of the two leads and projection from these values of right angle lines.

In the graphic method of plotting the angle α , illustrated by Fig. 5, we have made use of the principle of the equilateral triangle inscribed within the circumference of a circle upon which are marked the degrees from 0° at the right to $\pm 180^\circ$ at the left-hand end of the axis of the circle. Following Einthoven's original description rotation of the angle downwards and to the left, clockwise, constitutes a plus angle, whereas rotation upwards and to the left, counter-clockwise, constitutes a negative angle.*

The point marked by the intersection of the ordinate from the middle of the line representing Lead I and the horizontal axis of the circle represents the heart, and may further be regarded as the point p of the axis of potential difference, as illustrated in Fig. 1.

* This method of reading a positive or negative angle is at variance with the accepted custom in vogue as given by Wentworth and Smith, "Plane Trigonometry," Chap. V, p. 77, 1914.

If from each side of our equilateral triangle we project ordinates, at a distance of 1 mm. apart, assigning to those on either side of the center of each base line, corresponding to the Leads I, II and III, their proper positive or negative sign determined by the projection of our arrow $p-q$, then the point of intersection of any two of these ordinates, representing the value of e_1 , e_2 and e_3 under their proper sign, must coincide with the point q in our diagram Fig. 1. A line from the center H to this point of intersection corresponds to the manifest potential difference E , and will give us the direction of the axis of potential difference. By projection of this line to the circumference of the circle the angle α may be read off in degrees with its corresponding positive or negative value.

Utilizing the measurements of all three derivations in the terms of e_1 , e_2 and e_3 , under their proper sign, we shall find that with the physiological electrocardiogram our point of intersection for all three leads coincides very closely, and that in those instances with a conspicuous phasic difference the point of intersection will vary slightly, depending upon the ordinates employed, thus suggesting in a graphic way the extent of this phasic variation.

In the instances suggesting a ventricular preponderance, the values e_1 and e_3 should be used, and whenever the initial ventricular deflections are definitely diphasic in character, their corrected value should be determined by deducting the lesser amplitude from the greater.

Figs. 6, 7 and 8 may serve to illustrate the method of application of the principles stated above for determining the axis of potential difference in the heart.

In Fig. 6, which represents a physiological electrocardiogram, R_1 measures 9 mm., R_2 16 mm. and R_3 7 mm. in height. We may express these values in the terms of e , as $e_1 = +9$, $e_2 = +16$, and $e_3 = +7$, then $e_2 = e_1 + e_3$. If we follow the ordinate $+9$ from the side corresponding to Lead I to the point where it meets the ordinate $+16$ from the side representing Lead II, we shall find that the ordinate $+7$ representing Lead III intersects this point (see the small circle in Fig. 5 in the lower right-hand quadrant) and a line from the center H projected through this point of intersection to the circumference of the circle gives the direction of the axis of potential difference and the value of the angle α as $+55^\circ$ and approximately $30'$. Determining the value of α for this electrocardiogram by Einthoven's formula 5 we get a value of $+55^\circ$ and $52'$.

In Fig. 7, the initial ventricular deflections have the following values: $R_1 = 15$ mm., $S_1 = -1.5$ mm., $R_2 = 4$ mm., $S_2 = -9$ mm., $R_3 = 1$ mm., $S_3 = -16$ mm. We may ignore the values of S_1 and R_3 as they approach each other so closely, and utilizing R_1 and S_3 (e_1 and e_3) we repeat the steps outlined above and follow the ordinate $+15$ representing the Lead I to the point intersected by the ordinate -16 representing Lead III. A line from the center H through this point of intersection and projected to the circumference of our circle gives the value of the angle α as -34° . Determined by formula 6 the value is found to be -33° and $12'$ —an

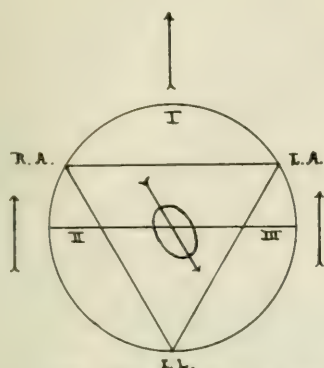


FIG. 2.—Illustrating the normal physiological direction of the axis of potential difference in the heart. The arrows indicate the direction of the initial ventricular deflections in the three leads. See Fig. 6 and description in text.

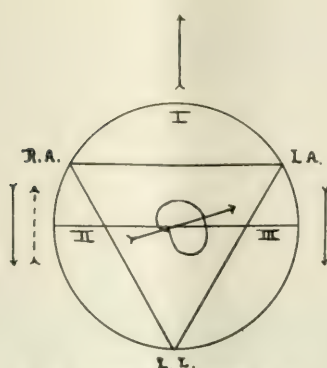


FIG. 3.—Illustrating the direction of the axis of potential difference in left ventricular preponderance. See Fig. 7 and description in text.

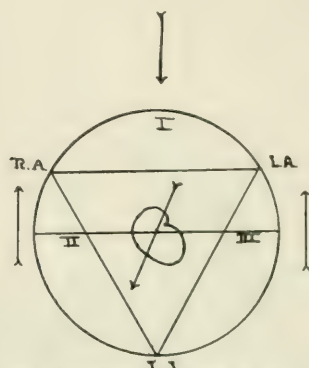


FIG. 4.—Illustrating the direction of the axis of potential difference in right ventricular preponderance. See Fig. 8 and description in text. Figs. 2, 3 and 4, modified after Pardee.

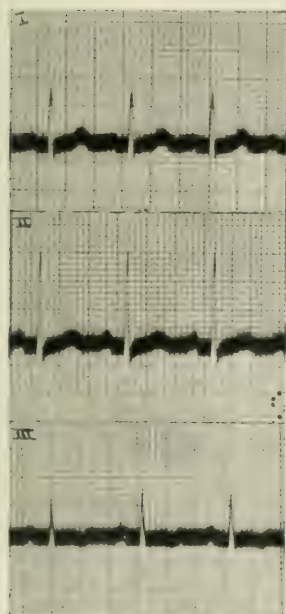


FIG. 5.—Illustrating the physiological electrocardiogram. The angle α measures $\frac{R}{S}$ and approximately so by plotting, and ϕ is $\frac{R}{S}$ and ϕ by formula 6.

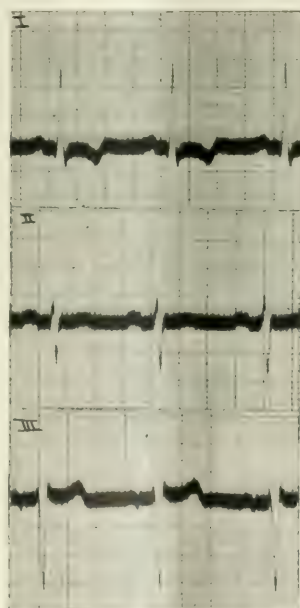


FIG. 7.—Illustrating left ventricular preponderance. The angle α measures $\frac{R}{S}$ and approximately so by plotting, and ϕ is $\frac{R}{S}$ and ϕ by formula 6.

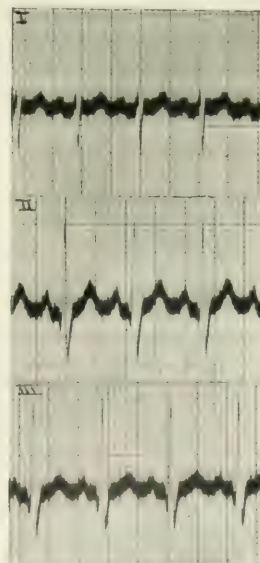


FIG. 8.—Illustrating right ventricular preponderance. The angle α measures $\frac{R}{S}$ and approximately so by plotting, and ϕ is $\frac{R}{S}$ and ϕ by formula 6.

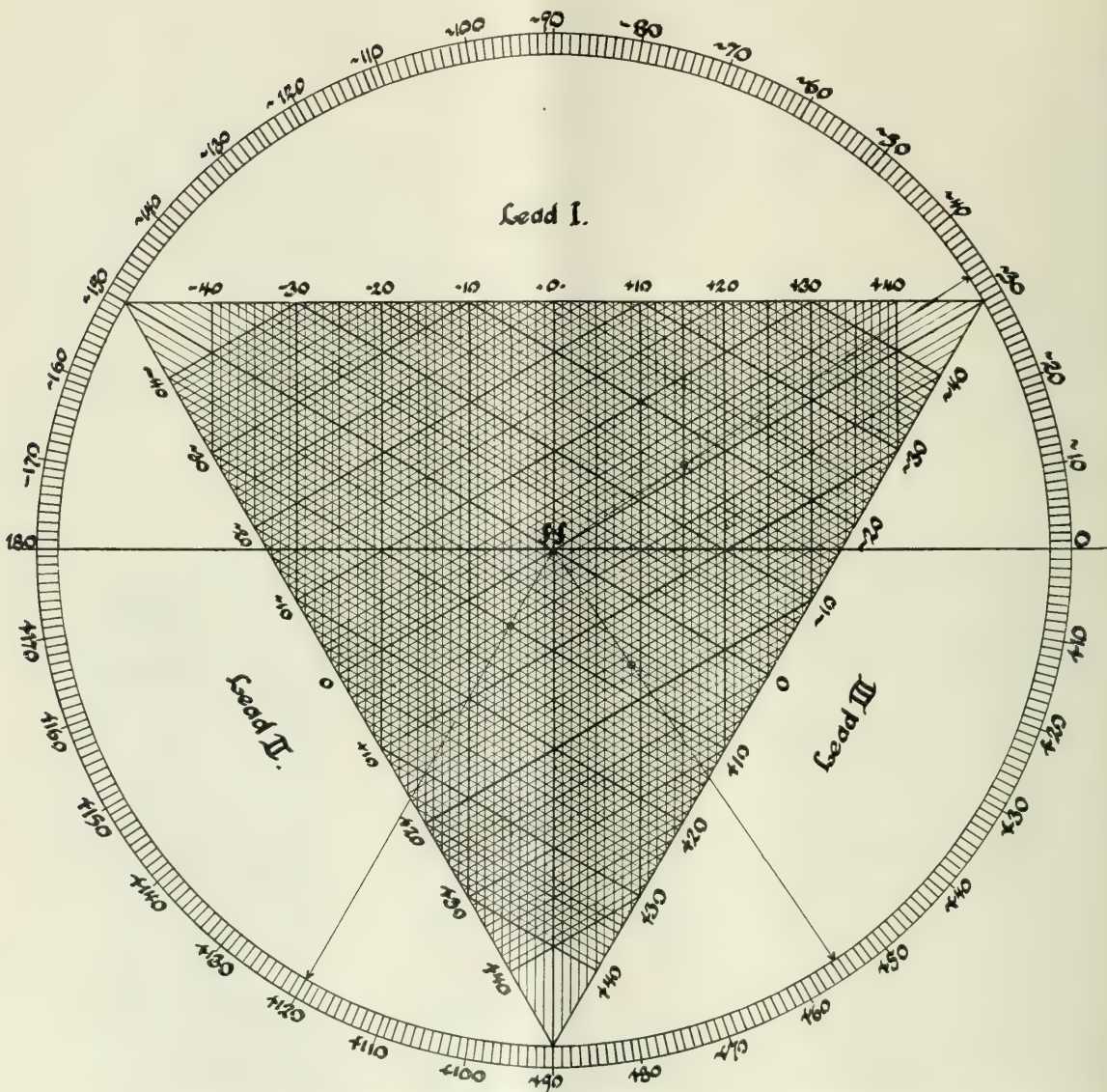


FIG. 5.—Illustrating the graphic determination of the angle α by means of ordinates projected from each side, or base, of the triangle representing the three leads. The ordinates are drawn to scale 1 mm. apart. The small circles in the figure represent the points of intersection of the ϵ values determined from Figs. 6, 7 and 8. The arrows projected to the circumference point to the plotted measurement of the angle α in degrees of these figures. See description in text.

angle known to be associated with left ventricular preponderance.

In a similar way we may plot the values of Fig. 8, which after correction for the slightly diphasic curves in Leads I and III are found to be as follows in the terms of e : $e_1 = -5$ mm., $e_2 = +10$ mm. Projecting our line from the center H through this point of intersection (see point in lower left-hand quadrant of Fig. 5) we find that the value of α falls between $+120^\circ$ and $+121^\circ$. Determined by formula 6 the value of the angle α for this figure is exactly $+120^\circ$, an angle known to be associated with right ventricular preponderance.

The points of intersection of the ordinates as given above are marked by the small circles in Fig. 5, and the arrows indicate the projection of the axis $p-q$ from the center H through these points of intersection to the circumference of the circle giving the direction of the axis of potential difference and the value of the angle α in degrees.

In addition we may determine graphically the true manifest value of the potential difference. As Einthoven has shown (*loc. cit.*, 1913), if the angle $\alpha = 60^\circ$ the manifest value E is equal to the deflection in Lead II, for this lead is then parallel to the electrical axis. If the angle α is equal to 0° or to $\pm 180^\circ$, $E = e_1$. If the angle $\alpha = +120^\circ$ or -60° , $E = e_2$. Referring

again to the examples given above, in Fig. 6, $E = 16.2$. In Fig. 7, $E = 17.8$. In Fig. 8, $E = 10$.

It is then plain that this diagrammatic usage of the equilateral triangle is available for accurate determinations of the direction of the axis of potential difference, the angle α and the manifest value E .

SUMMARY

We have emphasized the value of the fundamental principle of the equilateral triangle as applied in the interpretation of clinical electrocardiograms, and have illustrated graphically a simple method of procedure by which the value of the angle α may be quickly found.

BIBLIOGRAPHY

1. Einthoven, W.: *Pfug. Arch. f. die ges. Phys.*, 1908, CXXII, 558.
2. *Idem*: *The Lancet*, London, 1912, March 30, 853.
3. Einthoven, W., Fahr, G., and De Waart, A.: *Pfug. Arch. f. die ges. Phys.*, 1913, CL, 275.
4. Fahr, G.: *Heart*, 1912-13, IV, 147.
5. Williams, H. B.: *Am. Jour. Phys.*, 1914, XXXV, 292.
6. Pardee, H. E. B.: *Jour. Am. Med. Assoc.*, 1914, LXXII, No. 17, 1311.
7. Fahr, G., and Weber, A.: *Deut. Arch. f. klin. Med.*, 1915, CXVII, 361.

PHAGOCYTOSIS AND AGGLUTINATION IN THE SERUM IN ACUTE LOBAR PNEUMONIA; THE SPECIFICITY OF THESE REACTIONS AND THE REGULARITY OF THEIR OCCURRENCE

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In a previous article¹ the writer reported the results of some observations in a small series of cases on the activity of the serum developing, after crisis or lysis, in patients with acute lobar pneumonia. In agreement with the results obtained by most previous observers, it was found that the serum at this time usually developed a definite, though often feeble, protective power for mice, provided the test was made with the homologous strain of pneumococcus, isolated from the patient whose serum was being tested. This activity was not demonstrable in serum obtained during the active stage of the disease, either from patients who subsequently recovered or from those who died. It was further shown that, in a considerable percentage of the cases (six of 11 cases), a definite phagocytic activity could be demonstrated in the serum from convalescent patients. It was especially emphasized that this phagocytic activity has a significance quite different from that of an increase in opsonic index, as determined by the Wright method. In the latter, one uses heterologous stock strains of pneumococci of low virulence, which are at least moderately phagocytal in fresh normal serum. The strains studied by the writer, on the contrary, were (with one exception) of high virulence, and absolutely resistant to phagocytosis in fresh normal serum.

This phagocytic activity ran closely parallel with the protective power of the serum. It was entirely absent during the acute stage of the disease, and appeared only at or near crisis or lysis. It was not present in the serum of a fatal case. Like protective power it was manifested (with one exception) only toward the homologous strain of pneumococcus, and not toward those heterologous strains which were tested. It was further shown that in the two cases tested as to this point, phagocytosis *in vivo* ran parallel to that in the test-tube. In the peritoneal exudate of the protected mice, the pneumococci were ingested and dissolved within the leucocytes; whereas in the control mice receiving normal serum the organisms multiplied rapidly and remained exclusively extra-cellular.

In view of these facts, and of the part that phagocytosis has been shown to play in the activity of potent immune serum,² the writer felt justified in concluding that phagocytosis probably plays an important rôle in the immunity developed in man at crisis.

The series of cases was too small, however, to demonstrate the regularity with which phagocytic activity develops. Furthermore, the strict limitation of the activity of each serum tested to the homologous strain of pneumococcus was sur-

prising, in view of the findings of Cole and Dochez^{3,4} that most strains can be classified in a small number of groups. It, therefore, seemed desirable to extend these observations over a larger series of cases, and to determine more definitely the exact specificity of the reaction.

The results previously reported by the writer¹ were shortly confirmed by the independent observations of Lister⁵ in South Africa. Using a similar method, he also demonstrated in most of his cases definite phagocytic and agglutinative activity in the serum after crisis, when tested with the homologous organism. When these sera were tested with heterologous strains, phagocytosis and agglutination occurred in some instances, but in others they did not. By trying crossed reactions with the cultures and (convalescent) serum obtained from 20 cases of pneumonia, he was able to classify the organisms into five definite groups. The individual strains in each group he found to be serologically identical; while strains in different groups had no serological relationship to each other. In a subsequent article,⁶ he reported further similar observations confirming the regularity and absolute specificity of the reaction, and added several new groups to his classification.*

The development of agglutinins in the serum of patients with lobar pneumonia has been noted by numerous observers. Bensançon and Griffon,⁷ in 1900, reported positive findings in all but six of a series of 64 cases of pneumococcus infections of various types, of which 39 were lobar pneumonia. They obtained these results only by cultivation of the pneumococcus in concentrated serum from the patients, and failed to demonstrate any agglutinating activity when the serum was added to a broth culture of the organism. They found the activity most marked at crisis, and more effective toward the homologous strain than toward stock strains of pneumococci. Huber,⁸ using a similar method, obtained positive results in all of 10 cases of lobar pneumonia examined at or near crisis. Neufeld,⁹ in connection with a study of the agglutinating action of immune serum, mentions the fact that in five out of about 15 cases of lobar pneumonia examined, the serum at crisis, when added to a culture of the pneumococcus, caused marked agglutination of the organisms. This occurred with serum dilutions of 1 in 4, or 1 in 8, but not in higher dilutions. Gargano and Fattori,¹⁰ in a series of 63 cases, reported that the development of agglutinating activity in the serum was "an almost constant phenomenon." The sera were all active in a dilution of 1 in 2, but none in a dilution over 1 in 10. They also found the homologous organism more readily agglutinable than heterologous strains. Jehle¹¹ also reported positive results in all of six cases examined. However, his findings differ radically from those of other observers, in that he found the serum active in relatively high dilutions (1 in 20 to 1 in 80 and even 1 in 160); that the activity was well marked as early as the second or third day of the disease; that it showed no tendency to increase as crisis approached;

* As the earlier literature dealing with the subject of phagocytosis is summarized in my former article,¹ it will not be discussed here.

and that it disappeared entirely within from two to four days after crisis. More recently Chickering¹² has reported the demonstration of agglutinins in a 1 to 2 dilution of serum in 73.8 per cent of a series of 40 cases of lobar pneumonia. Most of the negative reactions were with serum from fatal cases. He found that the agglutinative activity developed only at or near crisis, and that it might be present only for a single day, or persist (*in vivo*) for several weeks. The agglutinating activity of the serum was strictly limited to organisms of the same type as that with which the patient was infected, but sometimes was more marked for the homologous strain than for a heterologous strain of the same type.

The method used by the writer was described in detail in the previous article,¹ hence only the essential points will be repeated here.

The cultures used were, with a few exceptions, those isolated in the routine study of the cases in the medical bacteriological laboratory of The Johns Hopkins Hospital, which have been reported by Mildred C. Clough,¹³ and by Sydenstricker and Sutton,¹⁴ and I am indebted to them for transfers of most of the strains.

Through the courtesy of Dr. R. I. Cole of the Rockefeller Hospital, New York, who kindly furnished us immune serum for the purpose, it was possible to determine the type of each of the organisms isolated. The phagocytic activity of the Type I and Type II immune sera has been tested with most of the organisms studied, and in some of the later cases observations have also been made with Type III serum, and with serum corresponding to Avery's Subgroups 2A and 2B.¹⁵

The leucocyte suspension was obtained by adding a few cubic centimeters of normal human blood to 1.5 per cent sodium citrate solution, washing three times in 0.85 per cent salt solution, and pipetting off the leucocytic cream after the last washing.

The bacterial suspension was prepared by carefully emulsifying a loop of growth in one or two drops of physiological salt solution. The suspension must be fairly dense to give the most clear-cut results.

Fresh serum obtained from the patient by any convenient method, usually venapuncture, was used in a majority of the cases, though it was found that in nearly all cases the activity of the serum persisted *in vitro* for several days at least. In some cases inactivated serum was also used.

Equal volumes of undiluted serum, bacterial suspension and leucocyte suspension were mixed and incubated in capillary pipettes at 37° C. The actual concentration of serum in the final mixture was, therefore, 1 in 3. The time of incubation varied from 15 minutes to two hours, depending on the strain of pneumococcus in question.

When a negative result was obtained, if possible, the test was modified by making the culture suspension directly in the serum to be tested, and by using defibrinated blood from the patient instead of a salt solution suspension of washed normal leucocytes. In this way the organisms were exposed to concentrated serum, instead of to a 1 in 3 dilution of serum. Corresponding control preparations were made, consisting of a

suspension of the organism in normal serum and defibrinated normal blood. Five cases which gave negative reactions by the first method were tested by this method; three gave positive results.

Smears from the mixtures after incubation were made on slides and stained with Hastings' stain (polychrome methylene blue). Suitably prepared films are free from sediment, and both the bacteria and the protoplasm of the leucocytes are clearly stained. As a rule, the margins of the capsules are sharply outlined and the capsular material is diffusely stained a bright pink, in contrast with the bluish-black color of the organisms.

As in the previous work, counts of the ingested organisms were not made. Only gross differences were regarded as significant. The degree of phagocytosis was recorded as (0) absent (or not to exceed five pair in 50 cells); (+) definite (about 100 or more pair in 50 cells); (++) strong; and (+++) maximal. Degrees of phagocytosis less than (+) in the test preparations were regarded as inconclusive.

In practically every case the tests were subsequently repeated, different specimens of normal serum and leucocytes being used to guard against possible errors.

This method is very simple, but in order to obtain reliable results certain precautions must be observed:

(1) The leucocyte suspension must be active. This can usually be determined by simple inspection of a fresh preparation under the high power. As pointed out by Neufeld,¹⁶ if the majority of the leucocytes show numerous filiform pseudopodia, one can be fairly sure that they are active. It is advisable also to set up a preliminary test with a strain phagocytal in fresh normal serum (not one spontaneously phagocytal). If a very marked phagocytosis has occurred after 15 minutes' incubation, the leucocytes are suitable for use. Attempts to compensate for an inactive leucocyte suspension by prolonging the period of incubation give unreliable results. The best results are obtained with fresh leucocytes. Phagocytosis is usually less active in older suspensions.

(2) The bacterial suspension should be fairly dense, and must be homogeneous and free from clumps.

(3) In every case controls must be made with normal serum, of the same age and condition as the serum under investigation, and all tests without exception be discarded if any appreciable degree of phagocytosis is present in the controls.

(4) The time of incubation should, if necessary, be adjusted for each individual strain, so that the test preparation will show as marked a degree of phagocytosis as possible without permitting any phagocytosis in the controls. For organisms of Types I, II and III, one hour is usually the optimum, though clear-cut positive results are often obtained after 15 to 30 minutes. If the results are negative or inconclusive because the degree of phagocytosis in the test preparations is slight, convincingly positive results may sometimes be obtained by prolonging the period of incubation to two hours. Rarely is anything to be gained by a longer period of incubation.

For organisms of Type IV and Atypical Type II, the period

of incubation should, as a rule, be shortened to 30 minutes, and in some cases to 15 minutes. If the incubation is too prolonged, there may be sufficient phagocytosis in the control preparation with normal serum to obscure the difference between these and the test preparations, a difference which would have been clear-cut after a shorter period of incubation. Too prolonged incubation may also obscure results, because it gives sufficient time for intracellular digestion of the ingested organisms, and because prolonged contact with the organisms seems to injure the staining properties of the leucocytes.

(5) The films must be properly spread and stained. The leucocytes and the larger bacterial clumps, if agglutination has occurred, will be found along the margins of the film, at and near the terminal portion. If the film is too thick, so that the leucocytes are heaped up or not well flattened out, observations are difficult. The presence in a serum of isoagglutinins active on the red cells present in the leucocyte suspension does not interfere with phagocytosis, but it makes it difficult to secure even films.

Before considering the results obtained with serum from convalescent patients, the behavior of the organisms in normal human serum should be discussed. In no instance were strains of Types I, II (typical) or III, on isolation, phagocytal in fresh normal human serum under the conditions outlined above. They also remained resistant to phagocytosis for at least several months while under cultivation on artificial media. The medium used was 5 to 10 per cent human blood agar; transfers being made at intervals of a week or 10 days. One Type II strain became very slightly phagocytal after two months' cultivation, and a second after cultivation for about a year. Type I strains seemed more resistant. Of three Type I strains followed for a long period, one became phagocytal in fresh normal serum during the third year of cultivation on artificial media; a second, during the fourth year; while a third, after four years' cultivation without intervening animal passage, is still not phagocytal.

The behavior of Atypical Type II and Type IV strains was variable, but most of those observed were less resistant to phagocytosis than were organisms of the fixed types. The majority of the Atypical Type II strains, and some of the Type IV strains, on isolation (from patients with pneumonia), were not phagocytal in fresh normal human serum after an incubation of half an hour, though after longer periods a slight degree of phagocytosis was occasionally observed. This resistance to phagocytosis was frequently reduced after one to three weeks' cultivation, so that the organism became phagocytal in fresh normal serum. In some cases the original resistance could be restored by animal passage. Such strains, after becoming phagocytal in fresh normal serum, were not phagocytal in normal serum which had been inactivated either by heating or by preservation for several days in the ice chest, and they usually retained this degree of resistance to phagocytosis after many weeks, and several even after two to three years of cultivation on artificial media.

Other strains, even immediately after isolation, were phagocytal in fresh normal serum, though resistant to phagocytosis

tosis in inactivated normal serum, even after considerable periods of cultivation. It was found that the phagocytic reaction of these organisms in inactivated homologous serum, either from an immune animal or from a convalescent patient, were nearly as clear-cut and just as specific as were those of the more resistant strains when tested in active serum. Two such cases (Nos. 40 and 41) are included in Table I. Such strains may possess a moderate virulence for rabbits and mice, and, as a rule, were not phagocyttable in fresh normal rabbit serum.

In examining (in inactivated serum) these strains which are phagocyttable in fresh normal human serum, it is, of course, imperative that the leucocyte suspension be very thoroughly washed in salt solution (at least three times) to remove as far as possible all traces of fresh serum. Absolutely complete removal is probably not possible, and, as might be expected, there was frequently a very slight degree of phagocytosis of these strains in the control preparations. This must be allowed for in interpreting the final results of tests made with these strains.

Finally, there is a group of Type IV organisms which are spontaneously phagocyttable, *i. e.*, they are phagocyttable in inactivated normal serum or in salt solution. They are, of course, entirely unsuitable for use in phagocytic tests, although, since some of them show no agglutination in normal serum, the demonstration of agglutinative activity in the homologous serum might be possible. In the course of this work I have examined 13 such strains, all isolated from the sputum or blood of patients with lobar pneumonia. In four of the 13 strains, all isolated from sputum cultures, it was definitely shown that the organism isolated from the sputum was not the etiological agent in the disease, but was probably an ordinary saprophytic inhabitant of the mouth, since the serum of these patients in convalescence acquired the power of causing phagocytosis and agglutination of stock strains of a fixed type (in two cases typical Type II and in two cases Atypical Type II strains). In one case a second attempt was successful in isolating from the sputum the Atypical Type II strain for which the serum had developed phagocytic activity.

Of the remaining nine, five were obtained only from the sputum (four by culture, one by mouse inoculation). The patients all recovered, and no further evidence was obtained confirming or disproving the relationship of the organism in question to the pneumonia.

In four cases, however, the strains were obtained by blood culture from patients subsequently dying of the disease. In three of the cases there were 2000 or more colonies per cubic centimeter of blood. The pathogenicity of the organisms in these cases can scarcely be questioned.

Although the primary object of this study was to determine the phagocytic activity of the serum, note was also made as to the occurrence of agglutination in the preparations, and a rough estimate recorded of the degree of agglutination present. With ordinary care in emulsifying the growth, it was easy to obtain homogeneous suspensions entirely free from clumps, with virulent organisms of the fixed types. In a large number

of tests no agglutination of these organisms was ever observed in normal human serum even when undiluted. In the active (convalescent) sera, however, clumping was usually a striking feature of the preparations. The clumps varied in size from groups of a dozen pair up to masses occupying a large part of an oil-immersion field. Of course, no clumping was regarded as significant unless the suspension was perfectly homogeneous, and unless the control preparations with normal serum were entirely free from clumps. The agglutinated masses of pneumococci, however, differed strikingly in appearance from the masses occasionally met with in poorly prepared suspensions. In the former, the individual organisms were more widely separated, and presented an appearance such as might be produced if the capsular substance between the organisms had been greatly swollen in the process of agglutination. This appearance has been described by Neufeld,⁷ Huber⁸ and others.

Equally clear-cut results were obtained with a majority of the Atypical Type II and with many of the Type IV organisms studied. With a number of cultures, however, which showed a sparse dry growth on blood agar, and in which the capsules either were small or were not demonstrable, it was difficult or impossible to secure satisfactory suspensions free from clumps. Some other strains acquired this characteristic after prolonged cultivation on artificial media. Such strains also occasionally showed some tendency to agglutinate non-specifically in normal or in heterologous serum, and they were, without exception, discarded. The majority of these organisms were spontaneously phagocyttable, and probably were saprophytic inhabitants of the mouth.

The results of the tests made with the serum of patients with acute lobar pneumonia are tabulated individually in Table I and summarized in Table II. With a few exceptions noted in the table, the homologous strain of pneumococcus was used in the test: Of 33 cases in which serum obtained at or shortly after crisis or lysis was tested with the homologous strain, isolated from the same patient, 28, or 85 per cent, showed definite phagocytic activity, while five, or 15 per cent, were negative. Of these five negative cases, in three only a single specimen of serum was examined, and only in a 1 to 3 dilution. Tests in concentrated serum (if tried) might have yielded positive results. Of five cases which gave a negative reaction on the first test in a 1 to 3 dilution of serum, three gave positive results when tried a second time in concentrated serum. To these 28 positive cases may be added six others (included in Table I) in which the infecting organism was not isolated, but in which the serum after recovery caused phagocytosis and agglutination of a stock strain of one of the fixed types (Type I, two cases; Type II, three cases; Type Atypical IIA, one case). Only three patients in the series (Nos. 13, 14 and 21) received serum treatment with Type I serum, and in the two cases (Nos. 13 and 14) giving positive reactions there did not seem to be any immediate association between the administration of the serum and the appearance of phagocytic activity in the patient's serum.

Of the 33 cases tested with the homologous strain of pneumococcus, 26, or 79 per cent, gave definitely positive agglu-

tion reactions. The two sera which showed phagocytic but no agglutivative activity were among the three relatively feeble sera which were active only in full concentration. These figures correspond quite closely with those reported by Chickering¹² and obtained by a different method.

This phagocytic and agglutivative activity appeared with equal constancy after infection with pneumococci of Types I, II and IV, and also in the only patient in the series with Type III infection who recovered.*

Serum was also examined from seven patients who later died of the disease, and the result was negative in six. The one case in which death occurred after serum activity developed will be discussed later.

In 18 of the 34 patients whose serum in convalescence was active in stimulating phagocytosis, tests were also made with serum obtained during the active stage of the disease. All were negative with three exceptions, and these three specimens were all obtained one day (or less) before the crisis. Of nine cases (eventually positive) tested 24 hours or less before the crisis, four were positive and five negative. Of nine cases tested about 24 hours after the crisis all were positive.

Very scanty data were obtained to indicate how long the activity of the serum persists in the body. In one case it disappeared within 11 days, but it was usually present on discharge, from 10 days to three weeks after the crisis. In one case (No. 27) serum obtained two years later still showed slight phagocytic activity and fairly marked agglutivative activity for a stock Type II strain.

We may, therefore, conclude that the serum is inactive during the acute stage of the disease, and that phagocytic and agglutivative activity develop only at or near the crisis, occasionally appearing shortly before it, but often demonstrable only after recovery has definitely set in.

The only instance met with which seems to constitute an exception to this rule is No. 44, Table I. This patient was a man aged 61, alcoholic, with arteriosclerosis and hypertension. He was admitted to the hospital on the fifth day of the disease with signs of consolidation in the right upper lobe. On admission (fifth day), a Type IV pneumococcus was isolated from the sputum and also from the blood (1 colony per cubic centimeter of blood). On the 13th and 14th days the temperature fell by lysis, and it seemed probable that the patient would recover. However, the temperature did not reach normal. On the 16th day it again became markedly elevated, and a high remittent fever of the "septic" type persisted till death on the 21st day. A Type IV pneumococcus was again cultivated from the blood on the 18th day (2 colonies per cubic centimeter). All three strains were found to be serologically identical. On the 19th day the heart was found to be dilated, and a systolic murmur appeared

at the apex. On this day the patient suffered a left hemiplegia. Nothing definite could be made out in the lungs or pleuræ to explain the recrudescence of fever. No autopsy was obtained. While it was not certain that the hemiplegia was not the result of a coincident cerebral hemorrhage, it was thought probable that a sepsis had developed, with an acute bacterial mitral endocarditis and a cerebral embolism.

The pneumococcus isolated from this patient was slightly phagocytal in fresh normal serum, but not in inactivated serum. The inactivated serum of the patient obtained on the fifth day caused no phagocytosis or agglutination of his organism, but a specimen obtained on the 13th day (during the remission), both in the fresh state and after inactivation, caused very marked phagocytosis and agglutination of this organism. A third specimen of serum obtained on the 18th day was equally active. This was two days after the recurrence of fever, and was after the reappearance of the organisms in the circulating blood. In this case, therefore, sepsis apparently ensued, despite the presence of phagocytic and agglutivative activity in the serum.

To determine the specificity of the reaction, a large number of crossed tests were made with the active post-crisis serum of each case, heterologous strains belonging to the same type and also strains of different types being employed. Table III shows results obtained with sera from patients recovering from Type I infections, and Table IV from infection with other types. In general, these data may be summarized as follows: A serum which is active on the homologous strain, will, as a rule, cause phagocytosis and agglutination of any other strain of the same type, but is entirely inactive toward strains of any other type. This differs from the tentative conclusions previously reported by the writer. In the former series of cases, phagocytic activity, in the six sera in which it was demonstrable, was strictly limited to the homologous strain of pneumococcus, with the single exception of one serum, which was also active on one only of several heterologous strains with which it was tested. In view of the findings in this present series the explanation for the previous results probably is that only two of the organisms examined happened to belong to the same type.

The serum from patients recovering from Type II infection showed no activity toward Atypical Type II strains (with the exception, possibly, of No. 27; *Los.*, *S.*; Table IV). Serum from cases of Atypical Type II infections acted only on members of the corresponding subgroup.

Case No. 14, Table I, illustrates well the specificity of these reactions. This patient was admitted with a lobar pneumonia which was proven by sputum and blood cultures to be due to an Atypical IIA infection. The serum shortly before crisis was inactive toward this organism, but shortly after crisis caused active phagocytosis and agglutination of it. Four days after crisis a second attack of pneumonia developed, a different lobe being involved, and a Type I strain was isolated from both blood and sputum. His serum at this time was inactive toward the Type I strain, though active toward the IIA strain. He had a second crisis on the eighth day, and after this crisis

* The sera from two recent patients recovering from Type III empyema, not included in this series, showed well-marked phagocytic activity, but no agglutivative activity. This activity was present only in the fresh serum, and was limited to the homologous strain of pneumococcus.

phagocytic and agglutinative activity for the Type I strain had also developed.

Serum from one of the three patients infected with a Type IV pneumococcus was active only on the homologous strain. That from a second case was equally active on the homologous strain and on one other Type IV strain from another case of pneumonia, serum from which could not be obtained for study. The third case also furnished a serum which was active in promoting phagocytosis, not only of the homologous strain, but also of one other Type IV strain, isolated from the spinal fluid of a case of pneumococcus meningitis. The demonstration, among a comparatively small number of Type IV strains examined, of two pair of serologically identical strains, is in conformity with the recent findings of Olmstead,¹¹ and indicates the probability that further study will reveal new types among the pneumococci now included in Type IV.

The serum of this last case (No. 27; Los., S.; Table IV) also caused phagocytosis of typical Type II strains and, less actively, of several Atypical II strains as well. This patient's serum four days before lysis was inactive toward the homologous Type IV strain, but was not tested at this time as to its activity toward a Type II strain, as this anomalous behavior of the serum was not anticipated. This is the only instance in the series in which a serum showed phagocytic activity toward a strain of a type different from that which was isolated from the sputum (except for four cases in which spontaneously phagocytizable mouth saprophytes were isolated from plate cultures). This might be explained either on the assumption that the patient had a double infection with a Type II and a Type IV organism, or that he had previously had a Type II infection, with persistence of the antibodies for Type II strains. The possibility of such a persistence of antibodies for a long period is demonstrated by the fact that a specimen of serum obtained from this patient two years later still showed slight phagocytic and well-marked agglutinative activity for Type II strains. The activity of this specimen of serum for the homologous Type IV strain could not be tested, as the strain had been lost.

The agglutinative activity of this serum was less specific than its phagocytic activity, in that it not only agglutinated those strains which it caused to be phagocytized, but several other Type IV strains as well. The agglutinative reactions of the Type IV strains, and of some of the Atypical II strains, as observed in these tests, were not as specific as were the phagocytic reactions.

A special effort was made to detect any possible quantitative serological differences between different strains belonging to Type I. In two sera (Nos. 1, T. A., and 5, M. M., Tables I and III), both of which were but feebly active, the homologous strain was somewhat more actively phagocytized than were the heterologous strains tested.* This is in accordance with the observations of Chickering¹² on agglutination in the serum

of convalescents. He reported that in several instances "the first organism to be agglutinated was the homologous strain, and only later was the stock strain agglutinated." Different strains may differ considerably in their phagocytability in the same serum. Thus, in one series of tests with stock Type I immune serum, strains S and R were phagocytized in 1 to 48 dilution; strains V and B in 1 to 24 dilution; while T and F were phagocytized only in a 1 to 12 dilution. When an active human serum was titrated in increasing dilutions with several different Type I strains, the highest titre was usually obtained with those strains which were most readily phagocytizable in any Type I serum rather than with the homologous strain. Although such specific strain differences undoubtedly exist, they must be relatively slight, and it is not always possible to demonstrate them conclusively.

The activity of immune serum of the various types on most of the strains studied was also observed, and some of the results are recorded in Tables IV and V. The same complete specificity is observed here, except in the agglutinative action of Type II serum on Atypical Type II strains. Type II serum in a concentration of 1 in 3 and with an incubation period of about 30 minutes caused agglutination of all the 25 Atypical II strains tested. However, Type II serum was much more specific in its phagocytic reactions toward these strains. With only two strains was any definite phagocytosis observed; and this was much less active than was the phagocytosis of typical Type II strains.*

The Atypical Type II strains were actively phagocytized and agglutinated by an immune serum corresponding to the particular subgroup to which they belong, but were not affected by serum corresponding to the other subgroup or to any strain not belonging to their subgroup.

This test, therefore, offers an additional simple method for the differentiation of typical Type II and the various Atypical II strains, and has proved to be of practical value in the case of certain Atypical II strains, which were agglutinated macroscopically in Type II serum in dilutions of 1 in 32, and even in 1 in 64, though somewhat more slowly than Typical II strains.

The existence of other undescribed subgroups among the Atypical II strains is indicated by the fact that an immune serum prepared with a strain from a case of empyema, which did not fall into either Subgroup A or B, caused phagocytosis and agglutination of one other Atypical II strain.

As to the properties of the active substance which stimulates phagocytosis in these human sera, the observations previously reported by the writer have been confirmed. They are in the main thermostable. In eight of nine cases tested, serum inactivated for 20 to 30 minutes at 56° C. retained its activity. When the heating materially exceeded this, either in duration

* Several other Atypical II strains, after their resistance to phagocytosis had been lowered by cultivation on artificial media for a considerable period, also acquired a slight degree of phagocytability in Type II serum. With the two exceptions noted, however, all strains when tested shortly after isolation were not phagocytizable in Type II serum.

* In two recent patients recovering from Type III empyema, not included in this series, the phagocytic activity of the serum was strictly limited to the homologous strain.

TABLE I

PHAGOCYTIC AND AGGLUTININATIVE REACTIONS IN THE SERUM OF PATIENTS WITH LOBAR PNEUMONIA. TESTED WITH THE HOMOLOGOUS STRAIN OF PNEUMOCOCCUS

No.	Name	Hospital medical number	Source of strain	Type	Result		Tests during acute stage			Tests during con- valescence			Titre of phagocytic activity of serum	Remarks
					C-crisis L-lysis D-death	Day of disease	Result		Days be- fore crisis, lysis, or death	Result		Days after crisis or lysis		
							Phag.	Aggn.		Phag.	Aggn.			
1	T., A.	35390	Sputum	I	L	21	+	0	4	1-1, +	
2	V., J.	35430	Sputum	I	C	15	+	+	1	+	+	18	1-3, 0	
3	R., C.	35482	Sputum	I	L	13	0	+	7	+	+	1	1-3, +	
4	S., J.	35517	Sputum	I	C	9	0	0	3	+	+	19	1-6, +	
5	M., M.	35628	Sputum	I	L	6	0	0	4	+	+	2	1-12, +	Serum had become inactive 11 days after lysis.
6	P., P.	35582	Sputum	I	C	6	0	0	1	+	+	11	1-3, 0	
7	P., C.	35682	Sputum	I	L	11	0	0	8	+	+	0	1-3, +	
8	M., W.	35601	Sputum	I	L	10	0	0	3	+	+	1	1-3, +	
9	McK., C.	35702	Empyema	I	L	7	+	+	30(?)	1-3, +	
10	R., J.	34902	Sputum	I	C	11	0	0	4	+	+	12	1-3, +	
11	G., N.	35274	None obtained	(I)	C	6	+	+	12	1-3, +	Tested with stock Type I strain.
12	B., C.	35681	None obtained	(I)	L	12	0	0	5	+	+	1	1-3, +	Tested with stock Type I strain.
13	W., H.	37336	Blood, Sputum	I	C	7	+	+	10	1-3, +	
14	W., G.	37356	Blood, Sputum	I	C	8	0	0	12	+	+	3	1-3, +	This followed 4 days after a IIA pneumonia. See No. 33.
15	T., C.	38976	Sputum	I	C	8	+	+	1	1-3, +	This followed 3 days after a Type II pneumonia.
16	B., H.	35628	Sputum	I	L	6	0	0	11	1-1, 0	Not tested till 11 days after lysis.
17	W., M.	35662	Sputum	I	L	7	0	0	2	0	0	2	1-1, 0	Clinically broncho-pneumonia.
18	M., S.	35504	Blood, Sputum	I	D	19	0	0	14	Pneumothorax following aspi- ration.
19	F., J.	35388	Blood	I	D	7	0	0	7	
20	J. W.	35308	Sputum	I	D	9	0	0	5	
21	J. W.	37409	Sputum	I	D	9	0	0	3	
22	S., F.	35346	Sputum	II	L	10	0	0	3	+	+	4	1-6, +	
23	M., T.	37419	Sputum	II	L?	2	+	+	7	1-12, 0	
24	D., H.	39040	Blood, Sputum	I	C	7	+	+	4	1-3, +	
25	C., J.	35341	None obtained	(II)	C	9	0	0	0	+	+	11	1-3, +	Type IV from sputum 8 days after crisis. Tested with stock Type II.
26	T., J.	35671	Sputum (IV)	(II)	L	9	+	+	1	1-3, +	Phagocytal IV from sputum. Tested with stock Type II.
27	L., S.	35661	Sputum (IV)	(II)	L	13	+	+	1	1-3, +	Type IV from sputum. Tested with stock II. See No. 41.
28	O., E.	37279	Sputum	II	L	9	0	+	4	1-3, 0	Not tested in concentrated serum.
29	W., H.	39103	Sputum	III	C	3	+	+	3	1-3, +	
30	C., C.	35506	Sputum	III	D	7	0	0	4	
31	H., G.	37200	Sputum	IIA	C	7	+	+	5	1-3, +	
32	B., W.	37328	Sputum	IIA	C	7	+	+	14	1-3, +	
33	W., E.	37356	Blood, Sputum	IIA	C	7	0	0	0	5	1-3, +	See No. 14.
34	H., B.	37334	Blood, Sputum	IIA	L	7	+	+	6	1-3, +	
35	S., T.	37248	Sputum	IIA	C	9	+	+	5	1-3, +	
36	McG., G.	37468	(See remarks)	IIA	C	8	+	+	3	1-3, +	Phagocytal IV from sputum. Tested with stock IIA.
37	J., H.	37674	Blood, Sputum	IIA	D	9	0	0	2	
38	E., R.	35806	Blood, Sputum	Atyp. II	C	10	0	0	7	+	+	0	1-3, +	
39	D., W.	37433	Sputum	Atyp. II	C	3	0	0	3	1-3, 0	Not tested in concentrated serum.
40	B., J.	35679	Sputum	IV	L	8	0	0	3	+	+	2	1-3, +	
41	L., S.	35660	Sputum	IV	L	13	0	0	4	+	+	1	1-3, +	See No. 27.
42	W., H.	37409	Sputum	IV	C	7	+	+	8	1-3, +	
43	N., A.	37610	Sputum	IV	L	4	+	+	3	1-3, +	
44	W., J.	35627	Blood, Sputum	IV	D	21	0	0	16	
45	B., W.	37335	Sputum	IV	L	8	0	0	5	1-3, 0	Not tested in concentrated serum.
46	N., H.	37205	Sputum	IV	D	8	0	0	?	

TABLE II

SUMMARY OF PHAGOCYTIC REACTIONS IN THE SERUM OF PATIENTS WITH LOBAR PNEUMONIA

Reactions with serum from convalescent patients (lobar pneumonia). Cases tested with the homologous strain				Additional cases tested with stock strains		Reactions of serum during acute stage, from patients whose serum eventually gave positive reactions				Reactions of serum from patients who subsequently died			
No.	Positive	Negative		Positive	No.	No.	Positive	Negative		No.	Positive	Negative	
Type I.....	15	13	2	2	14	11	3	8	4	0	0	4	
Type II.....	4	3	1	1	3	2	0	2	0	0	0	0	
Type III.....	1	1	0	0	1	0	1	0	1	0	0	1	
Type IV.....	6	5	1	1	3	3	0	3	0	0	0	1	
Type Atyp. II.....	7	6	1	2	8	2	0	6	0	0	0	1	
Total.....	33	28-85%	5-15%	6	34	18	13-17%	15-33%	8	1-12%	7-27%		

* These three specimens were obtained on the day before crisis.

or height of temperature, the activity was lessened or destroyed. The serum usually remained active *in vitro* for several weeks, though it gradually weakened in activity. In two cases, serum, which in the fresh state was feebly active, lost its activity after from two to four days. Nearly all the sera, however, remained active throughout the period during which they were under observation, which varied from a few days to four months.

If the serum had become inactive or feeble as a result of overheating, long preservation or dilution, the phagocytic activity could not be restored or increased by the addition of complement. The substance is, therefore, quite different from the active substances (opsonins) of fresh normal serum, and corresponds to the bacteriotropins as defined by Neufeld.¹⁴

The active substance was present in the serum in relatively small amount. In a majority of the sera tested as to this point, no phagocytosis occurred if the concentration of serum in the mixture was less than 1 in 3. In a few cases it was active in a 1 in 6 dilution, and in one case in a 1 in 12 dilution.

These bacteriotropins, as well as the agglutinins, were precipitated from immune serum with the euglobulin, on the addition of 36 volumes per cent of saturated ammonium sulphate solution. The euglobulin fraction of the precipitate, redissolved in salt solution and freed from an excess of ammonium sulphate by dialysis, caused marked phagocytosis and agglutination. The pseudoglobulin fraction of the precipitate, obtained by the further addition of saturated ammonium sulphate solution to give a concentration of 44 volumes per cent, was likewise redissolved and dialyzed, and was found to be inactive, as was the dialyzed supernatant serum from which the globulins had been removed. In this respect, therefore, the bacteriotropins resemble most other antibodies which have been similarly studied.

These bacteriotropins are probably not identical with the agglutinins. In two sera in which definite phagocytic activity was demonstrable, no agglutination whatever occurred. As a rule, however, the agglutinative activity of the serum was

more marked, was usually present in higher dilution, and persisted longer *in vitro* than did the phagocytic activity of the serum. In one case agglutinative activity was observed to precede the development of phagocytic activity. However, the observations with reference to this point were not sufficient to determine which type of activity is usually the first to appear.

SUMMARY

Of 33 cases of acute lobar pneumonia in which the phagocytic activity of the serum after crisis or lysis was tested with the homologous strain of pneumococcus, 28, or 85 per cent, gave definitely positive results. These results confirm and extend those previously reported by the writer.

In 26, or 79 per cent, of these cases agglutinative activity was also demonstrable.

In 18 cases in which definite phagocytic activity was demonstrable in the serum after recovery either for the homologous strain or for a stock strain of known type, tests were also made with serum obtained during the acute stage of the disease, and negative results were obtained in 15. The three sera which showed phagocytic activity were obtained 24 hours or less before crisis.

Serum was also examined from seven patients who subsequently died of the disease, and negative reactions were obtained in six. A positive reaction was obtained in one patient, who, after a short remission, died apparently of sepsis and endocarditis.

This phagocytic and agglutinative activity of the serum developed after the recovery from infection with pneumococci of all the recognized types. It was strictly limited to organisms of the same type as that with which the patient was infected, but, as a rule, was exerted equally well on the homologous strain and on heterologous strains of the same type. It is, therefore, specific as to type, but not specific as to strain, as the writer originally believed.

The agglutinative activity of the serum as observed in these tests paralleled closely the phagocytic activity. In the case

TABLE III
PHAGOCYTIC AND AGGLUTINATIVE REACTIONS IN THE SERUM OF PATIENTS RECOVERING FROM TYPE I INFECTION, TESTED WITH HOMOLOGOUS AND HETEROLOGOUS TYPE I STRAINS

Serum	Strain of pneumococcus—Type I																			
	Type I (stock)	Type II (stock)	T. A.	V. J.	R. C.	S. J.	M. M.	P. P.	P. C.	M. W.	McK.	R. J.	B. H.	W. M.	Sc.	Joh.	Fen.	McC.	Mt.	For.
Serum, Type I (immune)	+3	+3	0	0	+3	0	+3	+3	0	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3
Serum, Type II (immune)	0	0	+3	+3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Serum, T. A.	+3	+3	0	0	+3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Serum, V. J.	+3	+3	0	0	+3	+2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Serum, R. C.	+3	+3	0	0	+3	+3	+3	+3	0	0	0	0	0	0	0	0	0	0	0	0
Serum, S. J.	+3	+3	0	0	+3	+2	+3	+3	+3	0	0	0	0	0	0	0	0	0	0	0
Serum, M. M.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	0	0	0	0	0	0	0	0	0	0
Serum, P. P.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	0	0	0	0	0	0	0	0	0
Serum, P. C.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	0	0	0	0	0	0	0	0
Serum, M. W.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	+3	0	0	0	0	0	0	0
Serum, McK.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	+3	+3	0	0	0	0	0	0
Serum, R. J.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	+3	+3	+3	0	0	0	0	0
Serum, B. H.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	0	0	0	0
Serum, W. M.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	0	0	0
Serum, Sc.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	0	0
Serum, Joh.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	0
Serum, Fen.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3
Serum, McC.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3
Serum, Mt.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3
Serum, For.	+3	+3	0	0	+3	+2	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3	+3

The first figure in each column represents phagocytosis, and the second agglutination.

PHAGOCYTTIC AND AGGLUTININATIVE REACTIONS IN THE SERUM OF PATIENTS RECOVERING FROM INFECTION WITH TYPES II, III, IV, AND ATYPICAL II, TESTED WITH THE HOMOLOGOUS STRAIN, AND WITH HETEROLOGOUS STRAINS OF VARIOUS TYPES

[illegible]

The first figures in each column indicate phagocytosis and the second agglutination.

• No homologous or zwitterion was obtained in these three cases.

DIAGNOSTIC AND AGGLUTININATIVE REACTION OF ATYPICAL TYPE II STRAINS TESTED IN IMMUNE SERUM OF THE VARIOUS TYPES

[illegible]

The first figure in each column represents $\beta_{\text{agonist}}/10^4$, and the second agglutination.

* This serum was obtained from the patient after crisis. All other sera in this table were from immunized animals.

of Atypical II and of Type IV strains it was not so sharply specific as was the phagocytic activity.

This phagocytic activity is entirely different from a possible rise in opsonic index, in that it brings about active phagocytosis of a virulent pneumococcus, not at all phagocytizable in normal human serum.

The active substances in the serum also differ from the opsonins of normal serum in that they are usually thermostable; they usually remain active for several weeks in serum preserved *in vitro*; and when their activity is lost, they cannot be reactivated by fresh normal serum (complement). They are therefore qualitatively comparable with the bacteriotropins of potent immune serum.

In view of the facts: (1) That this activity of the serum develops in nearly all patients who recover, but only appears, as a rule, at or near crisis; (2) that it is limited to organisms of the same type as that with which the patient is infected; (3) that, as previously reported, the "phagocytic activity of the serum ran closely parallel with the protective power for mice, both in incidence, in time of appearance and in strict specificity as to the type of pneumococcus concerned"; and (4) that phagocytosis in the peritoneum of the protected mouse closely paralleled phagocytosis in the test-tube; it seems probable that this factor plays an important part in bringing about recovery in man.

The part played by agglutination in immunity to the pneumococcus in animals has been emphasized by Bull,¹⁸ and in all probability it is also an important factor in human immunity.

That other factors are also concerned is indicated by the death of one patient from sepsis, despite the previous development of phagocytic and agglutinative activity in his serum; and by the fact that in several instances pneumococci, which had been cultivated from the blood of patients dying of pneumonia, were phagocytizable in normal serum or even spontaneously phagocytizable in salt solution.

The clinical value of the test will not be great as a method either of diagnosis or of prognosis, since the reaction develops only when recovery sets in. In cases in which as a matter of scientific interest it is desirable to determine the type of organism concerned in a recent infection, the development of a positive reaction either with a stock pneumococcus of known type or with an homologous isolation, would furnish practically conclusive evidence that this organism was the etiological agent concerned in the disease.

REFERENCES

1. Clough, P. W.: The development of antibodies in the serum of patients recovering from acute lobar pneumonia. *Bull. Johns Hopkins Hosp.*, Baltimore, 1913, XXIV, 295-306.
2. Neufeld, F., and Rimpau, W.: Weitere Mittheilungen über die Immunität gegen Streptokokken und Pneumokokken. *Ztschr. f. Hyg. u. Infectiouskrankh.*, Leipzig, 1905, LI, 283-299.
3. Cole, R. I., and Dochez, A. R.: Report of studies on pneumonia. *Trans. Assn. Am. Physicians*, Philadelphia, 1913, XXVIII, 606-616.
4. Dochez, A. R., and Gillespie, L. J.: A biologic classification of pneumococci by means of immunity reactions. *J. Am. M. Ass.*, Chicago, 1913, LXI, 727-732.
5. Lister, F. S.: Specific serological reactions with pneumococci from different sources. *Johannesb.*, 1914, W. E. Horter & Co. S. African Inst. Med. Research., Pub. No. 2.
6. Lister, F. S.: An experimental study of prophylactic inoculations against pneumococcal infection in the rabbit and in man. *S. African Inst. Med. Research.*, Johannesb., 1916, No. 8, 1-57.
7. Bensançon, F., and Griffon, V.: Etude de la réaction agglutinante du sérum dans les infections expérimentales et humaines à pneumocoques. *Ann. de l'Inst. Pasteur*, Par., 1900, XIV, 449.
8. Huber, F. O.: Ueber Agglutination der Pneumokokken. *Centralbl. f. innere Med.*, Leipzig, 1902, XXIII, 417-421.
9. Neufeld, F.: Ueber die Agglutination der Pneumokokken und über die Theorien der Agglutination. *Ztschr. f. Hyg. u. Infectiouskrankh.*, Leipzig, 1902, XL, 68.
10. Gargano, C. and Fattori, C.: Sull' agglutinazione del diplococco; contributo di fatti e di osservazioni. *Riv. crit. di clin. med.*, Firenze, 1903, IV, 177, 193, 209, 225.
11. Jehle, L.: Ueber Pneumokokken-Agglutination mit dem Blutserum pneumoniekranke Kinder. *Wien. klin. Wchnschr.*, 1903, XVI, 917-919.
12. Chickering, H. T.: Agglutination phenomena in lobar pneumonia. *J. Exper. M.*, Lancaster, Pa., 1914, XX, 599-613.
13. Clough, M. C.: A study of the incidence of the types of pneumococci isolated from acute lobar pneumonia and other infections, and an analysis of the cases classified by types in regard to mortality, complications, associated diseases, bacteriemia, and leucocytosis. *Bull. Johns Hopkins Hosp.*, Baltimore, 1917, XXVIII, 306-311.
14. Sydenstricker, V. P., and Sutton, A. C.: An epidemiological study of lobar pneumonia. *Bull. Johns Hopkins Hosp.*, Baltimore, 1917, XXVIII, 312-315.
15. Avery, O. T.: A further study of the biologic classification of pneumococci. *J. Exper. M.*, Lancaster, Pa., 1915, XXII, 804.
16. Neufeld, F.: Bakteriotropine und Oponine. *In Handb. d. pathogen. Mikroörg.* (Kolle and Wassermann), 2. Aufl., Jena, 1912, II, 401.
17. Olmstead (Miriam): A preliminary report on the classification of pneumococcus IV. *Proc. Soc. Exper. Biol. and Med.*, New York, 1916, XIV, 29-31.
18. Bull, C. G.: The mechanism of the curative action of anti-pneumococcus serum. *J. Exper. M.*, Lancaster, Pa., 1915, XXII, 457-464.

THE DEVELOPMENT OF CROSS-STRIATIONS IN THE HEART MUSCLE OF THE CHICK EMBRYO

By MARGARET REED LEWIS

The results obtained by different observers in regard to the development of the cross-striations in muscle-fibers differ so decidedly that one is forced to question whether any one of the views presents the entire story. Even though the discus-

sion be confined to the development of this structure in one organ and to one form, as, for instance, the histogenesis of the myofibrils in the heart muscle of the chick embryo, it is found that, although the papers published are few in number,

they nevertheless differ fundamentally from each other. In an effort to determine, if possible, the reason for these differences, a careful cytological study of the development of the heart of the chick embryo was undertaken. For this purpose preparations of embryos varying in age from 10 myotomes to four days incubation were made by a number of different methods. The astonishing result of the study of these was that one particular procedure always resulted in the presence of complete cross-striations in the heart, whether in very young embryos (10 to 15 myotomes—about 28 to 30 hours), or in older ones (two to four days).

Heidenhain (1899), in his Fig. 13, showed that the heart of a goose embryo of 3 days incubation contained many completely cross-striated myofibrils of different thicknesses, which stained with varying depth of color with iron-hematoxylin. Schlater (1907) contests this point, and although he finds that a few cross-striated myofibrils are located in the heart of chick embryos as early as $2\frac{1}{2}$ days incubation, the pattern of these cross-striations is not the same as that given by Heidenhain. Even in embryos as old as seven days Schlater failed to demonstrate the z-band, although he presents figures of many long myofibrils extending through several cells. He is not the only observer who was unable to find this band: Rouget (1863), Wieman (1907), Mlodowska (1908), Kurkiewicz (1909), Levi (1916) and Bruno (1918) show no trace of it in any of their figures. Duesberg (1910), however, observed the z-band in the heart muscle, as well as in the skeletal muscle. He describes the development of the myofibrils only very briefly. He states that it takes place in the heart of the embryo chick in the same manner as in the skeletal muscle, except that the myofibrils of the former are differentiated very much earlier than are those of the latter, as he has observed completely cross-striated myofibrils in the heart as early as the third day. In his Fig. 5 (Duesberg, 1910), a section through a chick embryo of 11 to 12 somites, there are no myofibrils shown.

Rouget (1863), Kurkiewicz (1909), Levi (1916), and Bruno (1918) also distinguished the cross-striations at an early stage, but each of these observers demonstrates the same pattern as that presented by Schlater. The youngest embryo observed by Rouget was of 36 hours incubation. In his figures the myofibrils found at this early age have the same type of cross-striation as that represented for a four-day embryo. In neither is the z-band shown. Kurkiewicz depicted cross-striated fibrils in his drawings of the heart muscle of a $2\frac{1}{2}$ -day embryo. Levi (1916) described the occurrence of fibrils in fixed preparations of cells grown out from pieces of the heart of a three- to four-day chick embryo explanted in plasma. In his figures most of these fibrils are smooth, others are varicose and a few are cross-striated. The z-band, however, is lacking in all. The latter is also true for the observations of Bruno (1918) carried on in the same laboratory. Bruno, however, found rather long varicose fibrils in the heart of embryos of 10 somites. Although Meves (1908), previous to Duesberg, concluded that the fibrils of the heart muscle are differentiated from

mitochondria, he nevertheless failed to indicate the presence of cross-striated fibrils in the heart of young chick embryos.

Ferguson and Jordan (1916, Fig. 102, page 95), show a group of myoblasts from the heart-muscle syncytium of a 48-hour chick embryo. This figure contains no evidence of cross-striation, although at this age such structures are numerous. Instead there are present in the cell various black granules and long black or gray threads, stated to be "myochondria, mitochondria and myofibrils."

Wieman (1907), apparently the first investigator to study the histogenesis of the myofibrils in the heart muscle of the chick embryo, obtained results quite different from any of the above authors. By means of a special technic, he found a definite reticulum in the muscle-cell. This network (cytoreticulum) is largely concerned in the development of the cross-striations, and in order to accept Wieman's view in regard to the formation of the cross-striations it is necessary to acknowledge his premise that such a network exists in the muscle-cell. In the past few years it has come to be accepted by most cytologists as an established fact that such a reticulum is not normal. This has been shown for fixed muscle material by Duesberg, Luna, Meves and many others. Moreover, it has been demonstrated by Lewis and Lewis (1917) that the living muscle-cell is not reticular.

A consideration of Wieman's figures suggests a quite different conclusion than that arrived at by him. At 30 hours (a period when the heart muscle can be shown to contain many cross-striated fibrils) he depicts a somewhat round cell with no trace of cross-striation, but instead, a network (cytoreticulum). At 126 hours, at the time when the cross-striated fibrils are numerous, the cell is figured more elongated and with the network arranged in longitudinal bands. From these figures it is possible to conclude that the two cells represented the effect of coagulation under different degrees of stretching. However that may be, Wieman's paper is carefully worked out and seems to exhaust the subject from this particular standpoint, especially so in view of the fact that more modern studies of technic have determined that such a reticulum does not exist in the living cell, but is the result of coagulation. For this reason it is rather surprising to find that Congdon (1918) has taken the subject up again from a somewhat similar point of view. Instead of a cytoreticulum, Congdon (p. 147) expresses this structure in terms of "three systems of membranes each parallel among themselves which intersect to form hexahedral compartments." At all intersections of the three planes he claims to find small, uniform mitochondrial granules. It is questionable whether these granules are mitochondria, since he misinterprets several types of granules supposed by other observers to contribute to the formation of the fibrils. For instance, he claims that Godlewski (1902) found the mitochondria to be concerned in the development of the fibrils, when it seems evident from the fixatives employed by that author (sublimite, sublimite acetic, acetic alcohol, etc.) that all the mitochondria were probably destroyed.

Thus a review of the literature on the histogenesis of the myofibrils, confined to the narrow field of the heart-muscle of

the chick embryo, brings to light a number of divergent views upon this subject. The origin of the myofibril has been attributed to a row of granules (Kurkiewicz), to the differentiation of the mitochondria (Duesberg), to a network (Wiemann) and to a system of hexahedral compartments (Congdon). Most of the observers failed to demonstrate the *z*-band. Heidenhain and Duesberg found completely cross-striated myofibrils in the heart muscle as early as the third day. These two writers differ, however, in their view as to the origin of the fibril.

The experiments given below show that the complete cross-striations can be demonstrated to be present in the earliest heart, *i. e.*, about 10 myotomes or 28 to 30 hours' incubation. In other words, cross-striations are already present at the age when certain observers demonstrate the appearance of granules, the formation of a network, the elongation of mitochondria, etc., from which they claim that the cross-striated fibrils are later derived.

METHOD

When the heart of a young embryo (up to 3 days) is fixed under the microscope it can be seen that practically any method of fixation will show the cross-striated fibrils at some stage of the process. Many of the solutions, especially those containing acetic acid or other coagulative reagents, rapidly cause distortions which partially or entirely obscure the cross-striations. Zenker's solution without acid (potassium bichromate 2% + sodium sulphate 1% + corrosive sublimate 5%) with the addition of a little osmic acid just before using was found to be the most successful. However, the secret is not in selecting the proper solution, for any one of these may give poor results if an added factor, the extension of the muscle, is neglected. The heart may be extended in various ways—by injection, etc.—but the simplest and most easily controlled method is by means of the weight of the coverslip. The procedure for the chick embryo heart was as follows: The egg was opened, the blastoderm cut around and lifted off into a dish of Locke's solution. In this the vitelline membrane was removed, the blastoderm shaken free from yolk and floated yolk-side down upon a coverslip. If the preparation was to be stained, or if very clear cells were desired, the membranes were dissected away from around the heart. In the very young embryos (10 myotomes), in which the heart is only a short tube in the midventral line and it is impossible to determine to which side it will extend when subjected to pressure, the membranes on each side of the head were taken away, the excess fluid was removed and the coverslip then inverted on to a drop of fixative (Zenker without acid to which a little osmic acid had just been added) on a slide. This fluid was rapidly withdrawn by means of two pieces of filter paper until the weight of the coverslip slightly flattened the heart. Care was taken to avoid crushing the embryo. The preparation was at once studied under the microscope with the oil-immersion lens and No. 6 ocular. The cross-striated fibrils appeared rapidly and could be observed more readily in this way than when stained. Such preparations keep for days, provided the coverslip is sealed with vaseline to prevent drying.

For studies upon the living muscle the method was the same, except that a drop of Locke's solution was used in place of a fixing solution. In such preparations contraction continued for an hour or longer and no fibrils were formed.

When vital stains were used, these were added to Locke's solution. The heart was first injected on the coverslip with the solution containing the vital stain, and afterwards mounted in a drop of the same solution. In these preparations, also, the heart continued to contract and no fibrils were formed during that period. None of the preparations were sectioned, but were always observed in the total mounts, either living or fixed.

OBSERVATIONS UPON FIXED PREPARATIONS

It was difficult to distinguish the heart-muscle cells before the heart formed into a single tube (about 10 myotomes) and no effort was made to do so. At this early age it was already composed of an outer layer of flat cells, a middle layer of muscle-cells and an inner layer of endothelial cells. In the fixed preparations of the heart muscle, the cell boundaries could seldom be determined. The muscle tissue of the heart of the youngest embryo appeared to be more or less a syncytium. Certainly in the embryos of 12 myotomes and older there was no doubt but that the fibrils passed across several cells, and that the fixed tissue formed a syncytium.

MYOFIBRILS IN FIXED TISSUE

As the heart matures there is a gradual increase in the number of the fibrils which appear upon fixation. In the heart muscle of a chick embryo of 10 myotomes only a few fibrils were formed; in those of from 15 to 18 myotomes a number of such structures appeared; in those of from 20 to 22 myotomes the fibrils were numerous; while in older embryos the heart became full of fibrils, passing in every direction. They were of varying widths in all ages of heart-muscle tissue (Fig. 5). Occasionally they were very thick, at times almost the width of the cell (Fig. 3); but usually they were narrower, sometimes about the width of a mitochondrion. In the muscle of the older embryos the fibrils formed were more uniformly narrow threads, while in that of the young embryos there were great divergences. None of the extremely narrow fibrils described by Heidenhain were distinguished. That writer claimed that a higher power of the microscope always demonstrated a still more delicate fibril, until the magnification at his control was exhausted. This may be shown by means of sections, but was not evident in my preparations. The fibrils were most frequently straight or only slightly bent, but in certain places they became curved with the outline of the cell. They were never wavy or undulating, except in poorly fixed preparations. They extended for long distances across a number of nuclei and passed in various directions across each other. The fibrils possessed depth when focussed and were not difficult to observe; they were also found at different depths of the focus.

After many observations upon each of the embryonic ages enumerated above, it became evident that there was a gradual accumulation in the cell of some substance which appeared as



Fig. 1. A plot-graph of a track curve of 10 seconds in which a turn for $t = 1$ m/sec is associated with $\alpha = 0.5$ is represented in the heart.



Fig. 2. A photograph of a hatched embryo after 48 hours of incubation. The embryo had 22 myotomes. The heart muscle was full of cells, the atria were

[illegible]

Fig. 1. Curves showing the dependence of the α and β components of the vector of the electric field on the angle θ in a plane of the beam cross-section. The curves are calculated for $\theta = 0^\circ$ and $\theta = 90^\circ$.

TABLE 1. A normal mapping of \mathbb{Z}_4 from the right to 4 nodes where there is a unit that is the sum of the elements on the left (mod 4).



fibrils upon fixation. Whether these fibrils became cross-striated, varicose, or smooth, or whether they were broad or narrow, depended entirely upon the treatment to which they had been subjected.

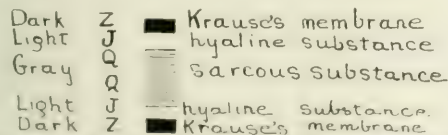
Stained preparations were much more difficult to control. Many of the stains diffused across the cross-striation; in other cases, much of the substance of the cross-striation, but not of the fibril, was dissolved out in the process of dehydrating and staining. The unstained preparations were so satisfactory that little experimenting was done with stains. Fig. 4, however, is drawn from a preparation successfully stained with iron hematoxylin.

The embryo was occasionally mounted in a drop of Locke's solution and the fixing solution permitted to penetrate under the edge of the coverslip. By this means the formation of the fibril could be observed under the microscope. In this way it was found possible to control the phenomenon and to produce various types of fibrils at will, thus showing that the form assumed is due to factors present during the fixation of some substance in the muscle tissue.

From the above it may be seen that by the use of Zenker's solution (without acid, and with the addition of a little osmic acid) and fixing with the muscle slightly extended, completely cross-striated fibrils are formed in the heart of the chick embryo at the early age of 10 myotomes. Many of the discrepancies of opinion shown by the above-mentioned writers were evidently due entirely to the lack of extension of the heart muscle, while others depended upon the fixing solution selected.

CROSS-STRIATIONS

The simplest method of designating these cross-striations seemed to be the dark band, the light band and the gray band. When the wing muscle of the house fly was fixed side by side with the embryo heart, there was a marked resemblance between the pattern of the cross-striations of the two tissues. Text Fig. 1



TEXT FIG. 1.—A diagrammatic representation of the pattern of the cross-striations found in the heart muscle of the chick embryo of 10 somites. The terms used to indicate the different parts of the cross-striations are placed opposite the part.

shows the manner in which the various terms used by other observers may be applied in these observations. The most pronounced part of the cross-striated pattern was the light band. This band was lighter than the cytoplasm and probably was composed of some substance which upon fixation did not become as dense as that of other portions of the cell. The dark band was much darker than any other structure of the cell and was probably quite dense. The gray band was practically the same as the cytoplasm. The dark band was never seen without the adjoining light band on each side. In certain rather round cells the fibrils could not be found, but the dark and light

bands were present and sometimes appeared to be scattered dark granules of uniform size, surrounded by a light area. From Congdon's figures it might be supposed that what was present in his material were not hexahedral compartments, but some such appearance as this. In his Fig. 2 the dark band, or granule, and the adjoining light bands are so spaced as to require little imagination to form them into such cross-striated fibrils.

Occasionally the cross-striations extended entirely across a cell without the presence of fibrils. These cross-striations were meager in depth and difficult to focus. The gray band was not noticeable as a special structure, but the regular space between the two light bands indicated its presence. The dark and light bands, however, were striking contrasts to other parts of the cell. Their appearance remained practically the same wherever found. The whole cross-striated fibril retained its characteristic appearance, whether widely spread out or only a narrow thread (Fig. 4).

The observations described above are based entirely upon fixed material. They show that the completely cross-striated fibrils can be demonstrated to be present at an age younger than that found by any other observer and also that they are already present at the time when these observers describe the presence of certain granules, threads, etc., from which the cross-striations are supposed to be derived later.

The presence of some substance which coagulates to form fibrils has been shown by Lewis (1919) to be characteristic of the smooth muscle, the heart muscle and the skeletal muscle. The same phenomenon is exhibited by these young embryos; *i. e.*, fibrils form upon fixation in the smooth muscle of the amnion, in the heart muscle and in the skeletal muscle.

In all probability the cross-striations are laid down in the heart muscle-cell coincidentally with the differentiation of these cells to form the muscle layer around the heart. This substance coagulates to form fibrils. It increases in amount in the cells during the development of the heart, with the result that the cross-striations become clearer and clearer, and the number of fibrils which can be caused to form becomes greater. With the increase in depth of this material along the surface of the muscle-cell the pattern of the cross-striations becomes less readily distorted upon the formation of the fibrils. Since it can be demonstrated by one procedure that the fibrils are completely cross-striated from their first appearance it is logical to assume that other methods fail to preserve these structures in their early form. For this reason, it is not necessary to discuss which theory so far advocated as to the origin of these interesting bodies is correct.

LIVING HEART MUSCLE TISSUE

Needless to state, the various aspects presented by the heart tissue as described above, including those observed by the several investigators mentioned, do not correspond to the appearance of the living tissue. This might readily be surmised if for no other reason than that one is dead and the other living. When preparations are made by the same method as that specified herein, except that in place of a fixing solution

a drop of Locke's solution is used, very thin living hearts are obtained and these continue to contract for an hour or longer. The most noticeable feature of such tissue is the complete lack of fibrils of any type.

The muscle-cells are not spread out into a flat layer as in the fixed preparations, but remain rather round or spindle-shaped, and because of this it is very difficult to determine whether there are processes between the cells or not. Certainly, the cells do not appear to form a marked syncytium.

In these observations on the living heart several embryos with 11 myotomes were studied, and as many as six of each of the different ages of older embryos (12, 15, 18, 20 and 22 myotomes). The muscular tissue of the hearts of embryos of from 12 to 15 myotomes appeared to be essentially the same. In that of older embryos trabeculae began to appear. The cell walls were distinguishable in places. Sometimes only a single cell in a given field showed contraction. Again, all the cells of a given region took part in the same contraction. The continued movement of the cells made it difficult to trace their individual boundaries. The tissue of the heart of older embryos (from 15 to 22 myotomes) appears to be more syncytial in nature. No preparation of a living heart was obtained in which contraction did not occur. The movement of these muscle-cells takes place so rapidly that it is almost impossible to be certain of the actual occurrences during the phenomena. In none of the hearts observed (about 50) was there any evidence of a slowing of the actual contraction. The rest periods became longer and longer, the number of contractions fewer and feebler, but the last contraction that took place was as rapid as any of the previous ones and in every case relaxation occurred after each contraction, even the last one. Rigor mortis was not observed.

MYOFIBRILS

No structure resembling the fibrils of the fixed preparation was present in the living heart muscle at any of the ages studied. In fact there were no long threads of any kind, not excepting the mitochondria. The latter did not extend farther than past the region of the nucleus, and were never seen to extend from one end of a cell to the other, or to pass from one cell to an adjoining cell. Certain preparations of pieces of the heart of four- to six-day embryos were used for comparison. No fibrils could be found even in this older heart muscle.

MITOCHONDRIA

The mitochondria were very abundant in the heart-muscle tissue of embryos of all stages up to four days' incubation. They exhibited active movement, bending, twisting and traveling in the cytoplasm. The most frequent forms were those of threads and rods. The longest filament, however, never extended the length of the cell. The long axis of a mitochondrion usually coincided with that of the cell. In round or only slightly spindle-shaped cells, the mitochondria seemed to lie in almost any direction. The outer cytoplasm of the cell was not invaded by these bodies.

When the heart of a 30- to 48-hour chick embryo was injected with Locke's solution, to which janus green has been added, and the preparation then mounted in a drop of the same solution, the mitochondria in the muscle-cells became stained. In such stained preparations the mitochondria appeared as bright blue threads, rods and granules. Certain portions of a mitochondrion occasionally stained more deeply than the remainder. There were no elongated blue threads, either smooth or varicose, extending the length of the cell.

NEUTRAL RED GRANULES

Preparations stained with neutral red in the same manner as that described above for janus green contained few small, red granules. When such a preparation was sealed with vaseline and kept under observation many red-stained bodies appeared in the cytoplasm. Similar bodies were observed in a few unstained preparations which had been kept under observation for a long time. The stained bodies were mostly in the form of round vacuoles, with one or more deeply stained granules; a few active pink filaments, with darker granules, were sometimes observed. Owing to their accumulation in such sealed preparations these neutral red vacuoles appear to resemble the neutral red bodies supposed by W. H. Lewis (1919) to represent waste products of the cell.

CROSS-STRIATIONS

The cross-striations are difficult to observe, either in the hearts of young embryos (11 to 18 myotomes), or in those of older ones (two days), without the most careful search. The most active cells contain the cross-striations as parallel bands of light and dark material. They extend only so far as the surface of the cell is in the plane of focus, becoming lost as soon as the vision penetrates below the surface. They may consist of only five or six parallel bands, or of as many as 10 or 12, again depending upon the plane of the surface. This is quite different from the fixed material, in which the cross-striated fibrils extend for long distances within the field of vision. In a few regions, such as along the side of the trabeculae, the cross-striations can be readily distinguished. Here they are arranged in the characteristic pattern, *i. e.*, dark band, light band, gray band, light band and dark band.

The cross-striations were most readily observed in the living heart by the aid of janus green. In such muscle tissue they appear frequently as a blue band with an adjoining light band. These were either close together or separated by a space where the gray band was indicated. The blue band was undoubtedly the dark band stained with janus green. In preparations which had been stained for some time the material between the two light bands (the gray band) also became slightly blue. In no instances were the cross-striations of the living material as marked as in the fixed preparations. This was largely due to the fact that they were never drawn into thicker bundles, *i. e.*, fibrils, but remained spread out over the surface of the cell.

SUMMARY

Thus it is seen that in the living cell cross-striations are present, but not fibrils. The cross-striations are very thin bands on the surface of the cell. They extend across the cell and are never in the narrow threads or fibrils. The fixation of the cell causes the formation of the surface layer into fibrils in which the cross-striations are drawn together into deeper bundles and thus become evident as sharply marked structures. In places where the pull on the surface of the cell is such that the latter is not coagulated into fibrils, the cross-striations remain spread out as thin bands across the cell (Figs. 2 and 4).

The complete cross-striations are present in the muscle of the heart of very young embryos (10 myotomes) much earlier than was supposed by other observers.

The physiologists have endeavored without success to formulate a theory, based upon the myofibrils, to account for the contraction of the muscle-cells. It is not surprising that such a theory has not proved satisfactory, at least in regard to the heart muscle, since the structure upon which it was based is not a part of the living heart-muscle cell, but only of the dead cell. In other words, a cell containing the structure upon which it was attempted to build the theory is not capable of undergoing contraction.

LITERATURE

Bruno, G.: 1918. La struttura del miocardio dell'embrione di pollo all'inizio della sua funzione contrattile. *Monitore Zool. Ital.*, XXIX, 53.

Congdon, E. D.: 1918. The embryonic structure of avian heart muscle with some considerations regarding its earliest contraction. *Anat. Rec.*, XV, 135.

Duesberg, J.: 1909. Ueber Chondriosomen und ihre Verwendung zu Myofibrillen beim Hühnerembryo. *Anat. Anz.*, XXXIV, 123.

Idem: 1910. Les chondriosomes des cellules embryonnaires du poulet, et leur rôle dans la genèse des myofibrilles. *Arch. f. Zellforsch.*, IV, 602.

Godlewski, E.: 1902. Die Entwicklung des Skelett- und Herzmuskelgewebes der Säugethiere. *Arch. f. mikr. Anat.*, LX, 111.

Heidenhain, M.: 1899. Beiträge zur Aufklärung der wahren Wesens der faserförmigen Differenzierungen. *Anat. Anz.*, XVI, 97.

Jordan, H. E., and Ferguson, J. S.: 1916. *Textbook of Histology*. New York, p. 95.

Kurkiewicz, T.: 1909. Zur Kenntnis der Histogenese der Herzmuskels der Wirbelthiere. *Bull. intern. de l'acad. des sciences de Cracovie*, p. 148.

Levi, G.: 1916. Migrazione di elementi specifici differenziati in colture di miocardio e di muscoli scheletrici. *Arch. per le Scienze Mediche*, XL, 1.

Lewis, M. R.: 1919. Muscular contraction in tissue cultures. *Contributions to Embryology* 35. Pub. 272. Carnegie Instit. Wash.

Lewis, W. H., and Lewis, M. R.: 1917. Behavior of cross striated muscle in tissue cultures. *Amer. Jour. of Anat.*, XXII, 169.

Luna, E.: 1913. Sulla importanza dei condriosomi nella genesi delle miofibrille. *Arch. Zellforsch.*, IX, 458.

Meves, F.: 1908. Die Chondriosomen als Träger erblicher Anlagen. *Arch. mikr. Anat.*, LXXII, 816.

Mlodowska, J.: 1908. Zur Histogenese der Skelettmuskeln. *Bull. intern. de l'acad. des sciences de Cracovie*, p. 145.

Rouget, C.: 1863. Mémoire sur le développement embryonnaire des fibres musculaires de la vie animale et du cœur. *Jour. de la Physiol. de Brown Séquard*, t. 6, p. 459.

Schlatter, G.: 1907. Die Myofibrillen des embryonalen Hühnerherzens. *Arch. f. mikr. Anat.*, LXIX, 100.

Wieman, H. L.: 1907. The relation between the cytotreticulum and the fibril bundles in the heart muscle of the chick. *Amer. Jour. Anat.*, VI, 191.

SPINA BIFIDA WITH ASSOCIATED DISTURBANCES IN A HUMAN EMBRYO 17 MM. LONG

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Human monsters at full term or in late fetal stages are seen, sooner or later, by almost every physician. Similar anomalies in very young embryos, such as the one described herein, are, however, not so well known. Dr. Mall¹ estimates the frequency of full-term monsters as 30 to every 5000 pregnancies and gives a resume of the protocols of 15 specimens showing localized anomalies (which he regards as the forerunners of monster formation) found among 1000 specimens in the Carnegie Collection of Human Embryos. This particular embryo (No. 1961, Carnegie Collection) is, however, of especial interest in view of the fact that, although having a menstrual age of only 79 days, it presents abnormalities of brain, spinal cord, viscera and skeleton, generally supposed to be characteristic

only of much older monsters. The clinical history is briefly as follows:

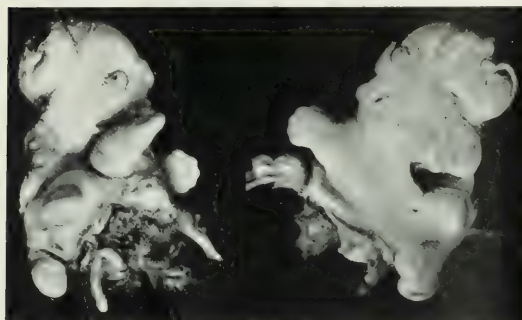
Parents white. Mother 42 years of age; has had five pregnancies, two of which ended at term, one child living (14 years), the other dying of "inanition." The third, fourth and fifth pregnancies terminated in abortion, the last furnishing the specimen under discussion. The last menstrual period began on August 19, 1917, and lasted four days; abortion took place on November 6. As both parents were very anxious for another child the possibility of mechanical interference may be excluded. There is no history of venereal disease. The only clinical symptoms which the woman presented were severe nausea and vomiting immediately before and during the abortion.

The gross appearance of the specimen is shown in the figure on p. 182, reference to which will enable the reader to understand better the following description. This is based upon a preliminary examination with a binocular microscope, supple-

¹ Mall, F. P.: On the frequency of localized anomalies in human embryos and infants at birth. *Amer. Jour. Anat.*, 1917, XXII, 49-72.

mented by examination under higher powers of serial sections through the embryo.

As seen in the ventral view, the embryo is normal above the level of the eyes. The latter are symmetrical, except that the left eye is placed slightly higher than the right. Microscopically, the lens of each eye is found to be hollow, the retina and choroid much macerated, and pigment is scattered throughout the vitreous. The external nares are represented by two pin-point depressions asymmetrically placed, and the lateral nasal processes are but feebly evidenced. The mouth is of normal width and in correct proportional position. It is gaping, however, and an enlarged tongue can be seen. The medial and lateral palatine processes are likewise visible. The ears show a well-marked helix, with no evidence of the original tubercles. There is a faint antitragus, and the primordium of the crus helix can be distinctly made out. Microscopically, the external auditory meatus and the Eustachian tube were



SPINA BIFIDA WITH ASSOCIATED DISTURBANCES IN A HUMAN EMBRYO
17 MM. LONG.

traced in section, but nothing could be made of the labyrinth. Taken as a whole, the face represents a development considerably in advance of that noted in the oldest of the human embryos described by Rabl in his "Entwicklung des Geschlechtes," which measured 14 mm. vertex-breech, and was estimated to be 36 or 37 days old. The face and ears, in comparison with other embryos in the Carnegie Collection, represent rather closely a stage of development corresponding to that of a normal embryo of the same length. Such embryos, according to the Mall curve, are about seven weeks old. From the degree of development of the head we may safely assume that 49 days is the maximum developmental age of this specimen. The discrepancy between this and the menstrual age, namely, 30 days, undoubtedly represents the length of time the embryo remained in the uterus after its death.

The arm buds show the transverse lines of division, and the contour lines of arm, forearm and hand. The hand pad shows the rays for five fingers, but progress toward digitation is not marked. Except for this, the arms correspond to the normal. The legs are disproportionately short for the general stage of development of the embryo, the foot pad showing practically no indication of beginning digitation. Study of the sections

shows that the cartilaginous shoulder and pelvic girdle are normal, but there is some stunting of the tarsals, metatarsals and phalanges of the foot pads.

There is a small genital tubercle behind which the clacal membrane has disappeared, leaving the sinus patent. The tail bud has been absorbed until only a blunt coccygeal eminence remains. There is some slight indication of a urethral furrow, whereas, according to the tables of Keibel and Elze, this should be "fairly deep" in an embryo of 17 mm.

Practically the whole ventral wall of the abdomen has undergone pathological changes, sloughed or been torn away, leaving the abdominal contents exposed. The viscera of thorax and abdomen show extreme maceration and histolysis, but their main outlines are well in evidence. In sections the alimentary canal may be readily made out; the mouth, pharynx, œsophagus, stomach, duodenum and coils of gut can be followed throughout their length. The larynx, trachea, main bronchi and macerated portions of the lungs could also be followed through the sections. The heart has suffered in the general maceration, but one chamber for auricles and one for ventricles can be clearly made out. The bulbus and first part of the aorta were traced, but no vessel was found leading from the latter. The liver was in a state of extreme maceration, but masses of liver tissue could be traced in sections, and also some vascular attachments connected with them.

The mesonephros is fairly well preserved, and there are discrete masses of badly macerated tissue occupying the positions where the suprarenals should lie. No evidence of a bladder or any of the urogenital ducts can be found. The same is true of the spleen and pancreas. There is widespread destruction of the vascular system; not even the main vessels can be traced with any sort of continuity.

From the dorsal aspect the most striking feature is the apparent failure of the medullary plate to close, a fact which was confirmed by microscopical examination. Caudad to the upper cervical region, and extending throughout the thoracic, lumbar and sacral regions, are two parallel rows of spinal ganglia on either side of the mid-sagittal plane, with discrete, scattered masses of nervous tissue between. Contrary to gross appearances, none of this tissue is naked, but all of it is covered by loose cellular tissue, undifferentiated and of irregular thickness. There is no trace of closure to form a cord. In the cephalic region as far back as the level of the eyes, closure seems to have taken place, and sections prove this to be the case, as the macerated remains of two cerebral hemispheres and a brain stem, covered with the same loose cellular tissue, are to be made out. The whole region, however, presents an irregular, bulging appearance indicative of an embryonic encephalocele. Meninges could not be found for the brain or other tissue of the central nervous system. In the region of the vertex there is a breach of continuity in the cranial vault, giving rise to an opening into the cranial cavity. This opening, upon a study of the sections, appears to be traumatic or the result of sloughing.

Twelve ribs and 30 vertebrae could be counted in sections, the latter with difficulty, owing to the fusion and twisting

of various centra. As determined from the sections, the vertebral axis shows the following points of interest: In the upper two-thirds of the back there is a deep cuneiform cavity, and exactly corresponding to this region is a very pronounced lordosis of the column. The middle of this region of lordosis marks a pivot point about which the posterior half of the vertebral column is twisted sharply to the right. In this way the ribs on the right side and the spinal ganglia are crowded together and appear in successive sections at the bottom of the depression. They are covered with loose cellular tissue. The cavity is due to the lordosis. In the region of the symmetrical depressions there is likewise a lordosis, and between these and the cavity the column is bent in the opposite sense—i. e., there is a slight kyphosis. The vertebrae show little or no evidence of neural processes, and of course no *membrana reuniens*. Technically speaking, therefore, we have an embryonic rachischisis and partial amyelia. Owing to the maceration and poor staining, the details of the chondrocranium could not be made out.

If due allowance is made for the extensive maceration, most of which probably occurred *in utero* after the death of the embryo, we are perhaps justified in asserting that the chief point of pathological attack lay in the axial skeleton and central nervous system below the brain. At any rate, it is here that we find its most important results. There is some stunting of the arms and legs, but not sufficient to be of any great significance, except that, had the viscera been early and seriously attacked, it is difficult to see why greater nutritional damage did not effect the extremities; for in spite of the fact that its aliment is furnished by the mother, the embryo must of necessity possess a correlated metabolism of its own. There is nothing to indicate that the viscera did not develop in a fairly normal way; at least the state of maceration does not suggest the contrary.

From the menstrual histories found among the records of the Carnegie Collection of embryos, it is more than probable that most of the pathological specimens are aborted within the first half of pregnancy, and, therefore, particularly if very young, their significance frequently escapes the notice of the practitioner. It follows that, in those cases in which the pathological involvement is not sufficient to cause the death and expulsion of the embryo, the latter will survive until the term or near term, and it is upon this limited group that the popular idea of the frequency of monsters is based. In the "Manual of Human Embryology," Dr. Mall has tabulated the comparative frequency of various types of monster formation at term and in aborted material, and finds a close parallelism between the two. The percentage of frequency of spina bifida is greater in the embryo, however, than at birth, indicating that the mortality is greatest in this variety of monster. A more careful examination of abortion material in the future will probably reveal numerous specimens like the one here reported.

That the cause of such conditions exists early in pregnancy is splendidly shown in the specimen above described. As pointed out by Dr. Mall, the popular conception that mechanical influences have an important bearing upon the formation of monsters has been overthrown by recent chemical experiments. The specific action of dilute salt solutions upon amphibian eggs, for instance, will produce spina bifida in a large proportion of the embryos. The trouble would seem to lie, therefore, not in the ovum itself, nor in the external mechanical influences acting upon it at a later date, such as amniotic bands which compress the umbilical cord, but rather in the impairment of nutrition associated with faulty implantation, or in the toxic influences arising from a diseased uterus.

BOOKS RECEIVED

United States Army X-ray Manual. Authorized by the Surgeon General of the Army. Prepared Under the Direction of the Division of Roentgenology. 219 illustrations, 1918. 12°. 506 pages. Paul B. Hoeber, New York.

United States, Department of Commerce, Bureau of the Census. Financial Statistics of cities having a population of over 30,000. 1917. 4°. 373 pages. 1918. Government Printing Office, Washington.

United States, Department of Commerce, Bureau of the Census. Birth Statistics for the registration area of the United States. 1916. Second annual report. 1918. 4°. 96 pages. Government Printing Office, Washington.

United States, Department of Commerce, Bureau of the Census. Financial Statistics of States. 1917. 4°. 129 pages. 1918. Government Printing Office, Washington.

Oxford Loose-Leaf Surgery. By Various Authors. Edited by F. F. Burghard, and Allen B. Kanavel. In five volumes. Over 1800 illustrations. Vol. I. 1918. 8°. 971 pages. Oxford University Press, London; American Branch, New York.

Practical Physiological Chemistry. A Book Designed for Use in Courses in Practical Physiological Chemistry in Schools of Medicine and of Science. By Philip B. Hawk, M. S., Ph. D. Sixth edition, revised and enlarged. With two full-page plates of absorption spectra in colors, four additional full-page color plates and 185 figures, of which 12 are in colors. 1918. 8°. 661 pages. P. Blakiston's Son & Co., Philadelphia.

The Hearts of Man. By R. M. Wilson, M. B. 1918. 12°. 182 pages. Henry Frowde and Hodder & Stoughton, London. Oxford University Press.

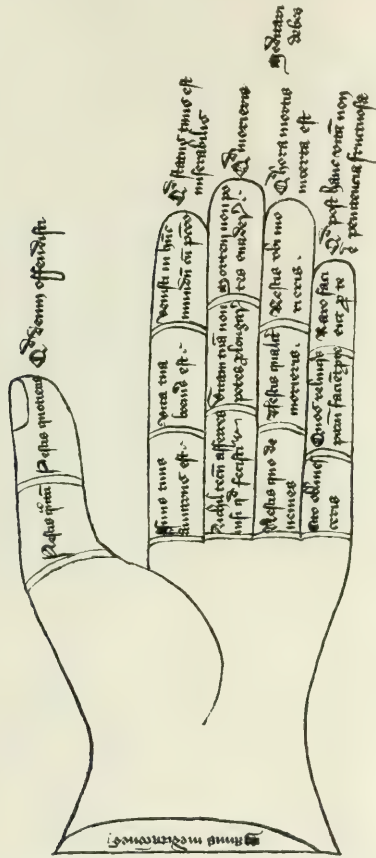
United States, War Department. Annual Report of the Surgeon General, U. S. Army, to the Secretary of War. For the Fiscal Year 1918. 8°. 735 pages. Government Printing Office, Washington.

United States, Treasury Department. Annual Report of the Surgeon General of the Public Health Service of the United States. For the Fiscal Year 1918. 8°. 373 pages. Government Printing Office, Washington.

THE MANUS MEDITATIONIS

By CHARLES SINGER, Oxford

Man alone among animals knows that he must die, and civilized man alone among the races of men. Yet we moderns, with all the discoveries of science, all the complexity of our social system and all the wonders of past history crowding thick upon us, certainly ponder far less than our forefathers



upon our inevitable end. With the men of the Middle Ages it was far otherwise. Their present world was a small thing compared to ours and but a vestibule of the life to come. *Mors janua vitae*. It was upon the life after death that their thoughts were fixed and upon death as its portal. Death was their obsession, and there were whole classes of men whose current thoughts were of little but death and thereafter.

Every possible device was invoked to keep death ever before the mind.

But the physician spends his life in a contest which he must always lose at last and for which life is the forfeit. He, at least, hardly needs to be reminded of the temporary character of this life. Yet not so, thought our ancestors. They did not hesitate to insert a *memento mori* even in a medical work.

Among the means adopted to keep mortality before men's eyes was the *manus meditationis*, a method of illustrating, by a tale of the fingers, the thinness of the partition that separates the living from the dead. The *manus meditationis* that we here reproduce was inserted by some fourteenth century scribe in a very valuable and interesting collection of illustrated medical tracts now in the Bodleian Library. The phrases are written along the five fingers of the hand, a phrase for each phalanx and a terminal one for the nail. The phrases form rough but not unmusical verse.

TEXT

MANUS MEDITACIONES (sic!)

- (1) Nescis quantum | Nescis quotiens | Quod deum offendisti
- (2) Finis tuus amarus est | Vita tua brevis est | Venisti in hunc mundum cum peccato | Quod status tuus est miserabilis
- (3) Nichil tecum afferes nisi quod fecisti | Vitam tuam non potes prolongare | Mortem non potes evadere | Quod morieris
- (4) Nescis quo deuenies | Nescis qualiter morieris | Nescis ubi morieris | Quod hora mortis incerta est
- (5) Cito obliuisceris | Quos relinquis parum facient pro te | Raro facient pro te | Quod post hanc uitam non est penitencia fructuosa

Meditari debes.

TRANSLATION

In rendering a translation of this simple text we would call attention to the use of the word *facient* in line 5. *Facere* has sometimes in mediæval Latin the special sense of "to make a prayer," "to say a mass," or simply "to pray"—*Orare est laborare*.

THE HAND OF MEDITATION

- (1) For that thou knowest not how greatly or how oft thou hast offended God,
- (2) For that thy end is bitter and thy life short, for that thou camest with sin into this world and thy condition is miserable,
- (3) For that thy deeds alone thou canst take with thee, for that thou canst not prolong thy life nor escape death, for die thou must,
- (4) For that thou knowest not whither thou goest nor place nor time of thy death, for the hour of death is uncertain,
- (5) For that soon forgotten thou wilt be, for that it is but little and seldom that thy relics will pray for thee, and for that after this life repentance availeth nought,

Therefore meditate.

BULLETIN

OF

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SOME MEMORIES OF THE DEVELOPMENT OF THE MEDICAL SCHOOL AND OF OSLER'S ADVENT

By HENRY M. THOMAS

In thinking of the early days of The Johns Hopkins University and Hospital and the development of the medical school, my memories begin with the founder—Johns Hopkins. As a small boy between 10 and 12 I sat on the same bench with Johns Hopkins many Sunday mornings at the Friends' Meeting on Eutaw and Monument streets. I cannot remember that he ever spoke to me, and I remember him merely as a rather unkempt old gentleman. At that time he had announced his intentions for his double bequest, had, in 1867, incorporated the two institutions that were to bear his name, had appointed his trustees, and had bought the site for the hospital. Gallo-way Cheston, the president of the university board; Francis T. King, president of the hospital board; Francis White, James Carey Thomas, James Carey, and other trustees, were also

constant attendants at the meeting, and it is pleasant now to think that in the congregation there were represented the founder, his trustees, and the rising generation which was to be benefited by the bequests.

Johns Hopkins believed that his wealth had been given to him for a purpose, and, to use a Friendly form of speech, that he would be "given to see" how to dispose of it. He had asked advice freely and much had been volunteered, and many of his advisers have claimed that they suggested the objects of his bequests and the forms which they should take, but I like to think that the wise instructions that he gave to his trustees were finally determined in meeting. The most important of these for the development of the medical school was his direction in a letter to the hospital board, dated March 10, 1873,

that "in all your arrangements in relation to this hospital you will bear constantly in mind that it is my wish and purpose that the institution shall ultimately form a part of the medical school of that university for which I have made ample provision by my will," so uniting forever the two bequests for the furtherance of medical education.

Johns Hopkins died on December 24, 1873, and in the early part of 1875 the trustees received the bequests and entered into active administration of the trusts. The first important decision of the university board was the wise and fortunate choice of Daniel C. Gilman as president of the university. He came to Baltimore May 1, 1875, and I can remember well the expectation and interest his coming aroused. He and his two daughters took apartments at the old Mt. Vernon Hotel, and for me a delightful friendship began.

Johns Hopkins chose his trustees well and left them untrammelled, and they in their turn gave President Gilman a free hand. They had already determined upon the establishment of a real university, which, as Gilman once said, was to supplement and not supplant existing institutions. In speaking of his first instructions which he received from the trustees, he says:

Often in private conversations and in official interviews, I was charged to hold up the highest standards, to think of nothing but the best which was possible under the limitations of the new establishment in a country where the idea of a university had not been generally understood.

In furtherance of these objects, President Gilman, in the summer of 1875, went abroad to visit the various universities and to consult with the leaders in education. Medical education was much in his mind, particularly the establishment of the laboratories and courses of instruction in the fundamental sciences which would be best fitted for the preliminary training of medical students. The field was almost entirely unbroken, and young men not yet 30 were selected for its cultivation—Rowland in physics, Martin in biology, and Remsen in chemistry. Rowland, although not then appointed to the chair of physics, had accompanied Gilman to Europe to aid him in the selection of physical apparatus and books. While on this journey he found time to publish some articles in the *Philosophical Magazine* which Gilman, with characteristic promptness and prophetic vision, dated from The Johns Hopkins University—the first university publications.

Gilman was inaugurated on February 22, 1876, and the university received students and began instruction in the fall of that year. Professor Huxley, who had taken much interest in the proposed biological department, and who had recommended a favorite pupil of his—H. Newell Martin—as its director, was in America and was asked to give an opening lecture. In this lecture he spoke of the importance of biological studies, and particularly their relation to a properly organized medical course. My father, who had selected me as the son most available upon whom to experiment with this new method of medical education, saw to it that I attended Gilman's inauguration and Huxley's opening lecture. I have no recollection of the inaugural exercises, but I do remember

hearing Huxley at the Academy of Music, principally, I think, on account of the storm of protest that followed. This protest was directed against the emphasis which the new university appeared to be giving to scientific research, especially in biology, even the study of which was thought at that time to be little less than impious, and was focused on the fact that Huxley, the great champion of science, had been asked to speak and that the lecture had not been ushered in by prayer. I believe that Mr. King and my father, both devoted religious workers, were responsible for this last circumstance. They certainly were astounded by the public reaction to this entirely consistent Quaker procedure.

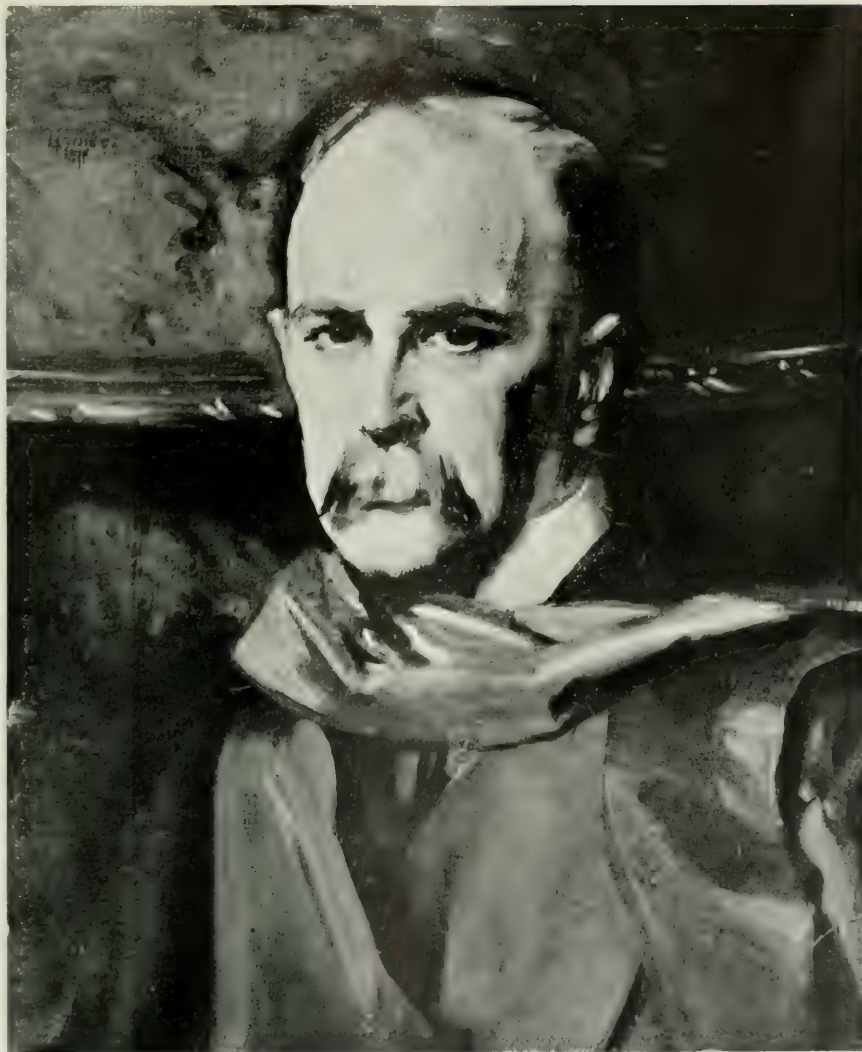
Following the advice of Huxley and others the chemical-biological course was designed, and was recommended to those students who intended to take up the study of medicine; indeed, it was also called the preliminary medical course. It was from the first the design of the university to establish the full medical course as soon as the hospital should be completed, and much thought was given to it. Martin and Remsen were recognized as forming the nucleus of the medical faculty.

At the opening of the fourth academic year, September, 1879, Professor Acland, then Regius Professor of Medicine at Oxford, was expected to give a lecture embodying his advice as to the proper co-ordination between the university and hospital in the organization of an advanced medical school. Unfortunately, on account of illness, he was unable to deliver the address. His views, however, have been preserved in a letter to the university and hospital authorities. How surprised he would have been had he been told that it was from this unborn medical school that his successor at Oxford was to be chosen!

In the early days the university was a small, compact body, made up, for the most part, of a young, active faculty, surrounded by a group of advanced workers, called fellows, and other post-graduate students, and a few rather over-powered undergraduates. Every encouragement and opportunity was given to research and to prompt publication of work accomplished. There was the closest sympathy among all the departments, and everyone knew and sympathized with the work of the others. It was naturally around Martin that the idea of the medical school germinated, and a more inspiring teacher it would be hard to imagine. Besides the regular biological courses, he gave lectures to medical students and practitioners of the city, and graduates in medicine entered his laboratory for special work.

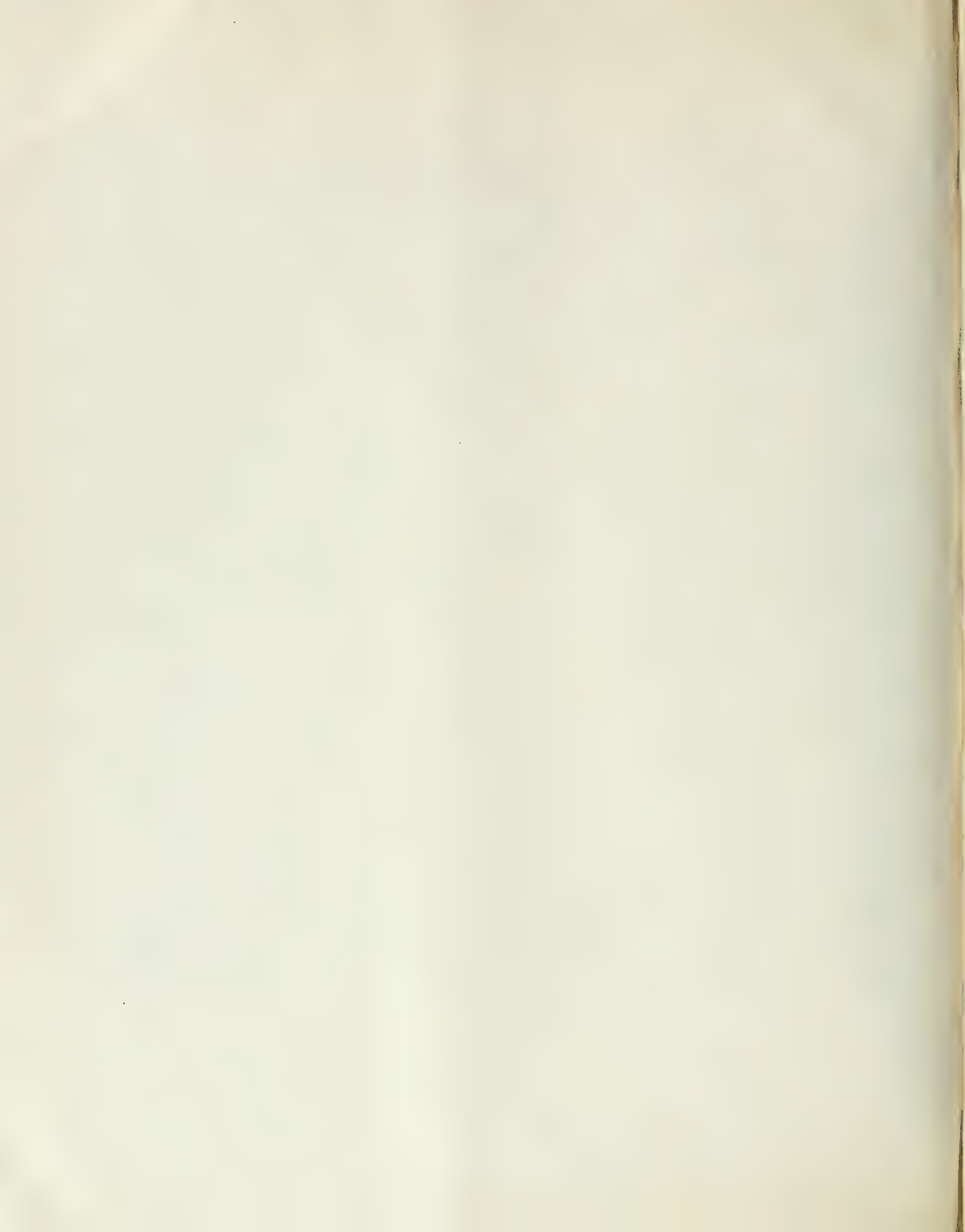
The emphasis which the university had put upon men in contrast to buildings had permitted it to function at once, and to strike a remarkable pace in a very short time. With the hospital it was different; buildings were absolutely essential, and even though Johns Hopkins before his death had instructed his hospital trustees to begin work, time was necessarily consumed in the formation of plans, so that it was not until June of 1877 that these were adopted and the excavations were begun.

The choice by the hospital board, in 1876, of Dr. John S. Billings, surgeon of the United States Army, and librarian



WILLIAM OSLER IN 1906.

Reproduction of original.



of the surgeon-general's office, as their medical adviser was most fortunate, both as to the construction of the hospital buildings and as to the future of the medical school. Dr. Billings was much in Baltimore, and his encyclopedic knowledge of things medical was always at the service of the university as well as the hospital. He supplemented Gilman, and made with him a remarkable team. He was attached to the university academic staff as a lecturer on the history of medicine and municipal hygiene, although I do not think he gave many lectures until after the opening of the hospital.

Among the physicians who were attracted to Martin's laboratory was Wm. T. Councilman, who began work in 1878, just after having received his medical degree from the University of Maryland, and who, after his return from Europe in 1882, was made a fellow by courtesy, and was appointed associate in pathology in 1884. He busied himself about medical problems, gave some courses in special subjects, and lectured at the University of Maryland on pathology.

In 1879, Wm. H. Howell came from the Baltimore City College and entered the chemical-biological course and began a career which was to mean much to the university and medical school. He soon became a favorite pupil of Martin's, and after receiving his bachelor's degree, he was made in quick succession a fellow, an assistant, and then, in 1885, an associate in biology, having received his Ph.D. the year before. He resigned from the university in 1889, to return again as professor of physiology at the opening of the medical school.

I, in my capacity as experimental animal, was entered in the university the same year, and I can well remember Howell as the model student and also on the football field where he made up for his light weight by the accuracy and neatness of his tackling.

I look back upon my course at the university with the greatest pleasure. To have been under such men as Martin, Remsen, and Hastings in physics, to have read Shakespeare with Sydney Lanier, and to have heard the lectures from the noted men who were constantly coming to the university, could not help being stimulating to a youth even though over-occupied with many athletic pursuits. It had been hoped by those of us who took the preliminary medical course that at its completion the university would have started its medical school, but this was not to be. The buildings of the hospital were going up very slowly, and as there seemed no immediate prospect of their completion, we were forced to go elsewhere for our medical instruction.

While at the University of Maryland, I attended Dr. Councilman's first lectures on pathology, and also took a course with him in the biological laboratory in the histology of the nervous system. We had excellent professors at the University of Maryland, but it was the old lecture system, the only laboratories being the dissecting room and a newly established chemical laboratory. The students had practically no chance of getting close to patients, and I was graduated without ever having been instructed in physical diagnosis, and I received the prize in obstetrics without ever having seen a woman in labor! I took my medical degree in 1885. By this time the

university was on the point of establishing its medical department. In the register for 1883-1884 it is announced that "The medical department of the university is soon to be organized. Its plan is receiving the constant attention of the trustees, and it will be made known before the completion of The Johns Hopkins Hospital. The nucleus of a medical faculty has been instituted as follows: The president of the university: J. S. Billings, M. D., lecturer on hygiene; W. H. Welch, M. D., professor of pathology; Ira Remsen, M. D., professor of chemistry; H. Newell Martin, M. D., professor of physiology."

In this somewhat casual way, the university announced the epoch-making facts that it had recognized pathology as a full university subject, and had appointed Dr. Welch to fill the chair. The first was the natural development of the university idea in medicine, and the credit of the second has been claimed, in a friendly rivalry between the university and the hospital, both by Gilman and by Billings. However that may be, no other choice now seems conceivable.

Dr. Welch's appointment was the first one that had to do with practical medicine, and I remember my father's enthusiasm over it, for with it he felt that the university had made a wonderful beginning in medical teaching. What a wonderful beginning it was he was to learn later!

Welch gave his first course of lectures in Hopkins Hall in February and March, 1886, on microorganisms in disease. The hospital trustees allowed the university to furnish the autopsy house as a pathological laboratory, and so the first of the hospital buildings to be used was dedicated to the common purpose of the two trusts. Dr. Councilman had been appointed an associate in pathology, and courses of instruction were started on November 1, 1886. Halstead came from New York to work in the laboratory and Mall was appointed the first fellow. Other students gathered, most of them graduates in medicine, and when I returned from Europe at the end of the year I joined the group. Those early days have often been described, and it was, indeed, a rare privilege to have taken part in them. As the hospital was not yet opened, the institution had to depend upon other sources for its autopsy material. This was obtained for the most part from the City Hospital at Bay View. In the reorganization of this charity, The Johns Hopkins University had assumed the care of the insane, and my father, Dr. Councilman and I were appointed visiting physicians. Dr. Councilman was also pathologist.

At this time everything seemed to point to the early opening of the full medical school. The buildings of the hospital were practically finished, and there seemed to be no reason why they should not be shortly opened. The university authorities were completing their plans and Welch was on the spot. It was just at this time that financial calamity overtook the university. The Baltimore and Ohio common stock, of which the university had nearly 15,000 shares, dropped its dividend from 10 to 8 per cent in 1886, to 4 per cent in 1887, and ceased paying the next year; the university was struggling for life and could not take on new obligations, so that the plans of the medical school were indefinitely suspended. The hospital income had not been affected as it was derived almost entirely

from real estate, and there had been no inroads on the capital by the erection of the hospital buildings. It had, indeed, increased, and the hospital had now become the rich member of these organically joined twin bequests.

The time had come for the hospital to take up the work, but for it to begin to function, men had to be found to organize the various clinical departments. Above all, a physician-in-chief had to be appointed and everything depended upon the choice. The question was anxiously discussed by the two boards of trustees and their advisers, and the little band of students in the pathological laboratory discussed the question with critical, impotent anxiety. Now that adversity had fallen on the university, what hope was there that the unbroken series of phenomenal appointments could continue? Where could a clinician be found to match Gilman, Billings, Martin, Remsen, and Welch, and if found, would such a man come now that the opening of the medical school in the near future was less than probable? We doubted, but we did not at that time know Dr. Osler and how impossible it would have been for him to have refused to add his strength to the endeavor to bring to fruition the long-nourished idea of a real university medical school. He has given an account of his reaction to the proposal. In speaking of Billings' visit to him in Philadelphia, he says: "Without sitting down, he asked me abruptly, 'Will you take charge of the medical department of The Johns Hopkins Hospital?' Without a moment's hesitation I answered, 'Yes.' 'See Welch about the details; we are to open very soon. I am very busy to-day; good morning,' and he was off, having been in my room not more than a couple of minutes."

The appointment was made in the fall of 1888, and he was to begin his service at the opening of the hospital, which was announced for May, 1889. It soon became evident that although it was easy to announce the opening day, it was quite another thing to get the complicated mechanism of the hospital organized and ready to function. In this emergency the hospital appealed to the university and induced Gilman to assume the task. The work was colossal and the time was short, and it speaks volumes for the estimation in which Gilman's organizing ability was held that no one doubted the result.

The formal opening occurred on May 7, 1889, and Osler, with his satellites, took his place as our guiding star. He brought Lafleur from Montreal, Scott and Toulmin from Philadelphia, and those of us who were able to do so joined the ever-increasing group.

The hospital annexed Welch with his already organized department of pathology. Halsted was given charge of the surgical department and the organization of the dispensary, Kelly was brought in June from Philadelphia to take charge of gynecology, and in August Dr. Hurd, as superintendent, took over from President Gilman the direction of the hospital.

The opening of the hospital was for the trustees, the faculty, and above all for us expectant, impatient medical novices, the beginning of the fulfillment of long-suppressed desires. For me the reality far surpassed the fantasy of my dreams. In the association that was to follow, which for my part was as close

as I could make it, Osler as a physician, teacher and friend, constantly raised my preconceived ideal. Memories of this time overwhelm me.

The dispensary was opened first and patients were admitted to the wards from it, and Osler, surrounded by a few of us, himself wrote the first dispensary history. Until the wards were full he was constantly in the dispensary, organizing the various subdepartments of medicine, for it was an unique feature of the system that the services were continuous, and that the various special departments were grouped under either medicine or surgery. As it was in the early days of the university, so it was with the hospital at the beginning. Workers formed a closely united body. All that happened was of interest to each of us. On the medical side Osler radiated by his example and personality constant stimuli to careful clinical work and investigation along all sorts of lines. He pointed out problems, encouraged everyone in what he desired to do, and was more than liberal in his commendation of work done. His absolute generosity threw open his whole clinical material to the use of any one who had a problem. He urged and assisted in the publication of the results, and saw to it that the young men got the whole credit of the work when often it should have gone to himself. Is it to be wondered at that such a chief has such devoted followers?

The Medical Society, the Journal Club, the Historical Club, and other associations, were organized in quick succession. Post-graduate courses were given, but the medical school of the university seemed as far from beginning as ever. The university trustees were not unmindful of the question, and some of them in spite of the depleted income, were constantly urging the establishment of the school. I have found among my father's papers the notes of an earnest appeal on the subject which he appears to have made to the Board of Trustees in May, 1890. Certain women, several of whom were daughters of trustees, who had from the first unsuccessfully sought admission for themselves and other women to the university, and who had been told that it was planned to admit women to the medical school when it should be established, collected money and offered \$100,000 to the trustees on condition that it should be used to help the establishment of a medical school to which women should be admitted on the same terms as men. On October 29, 1890, the trustees made a minute accepting the gift, with the proviso, however, that the university should not establish its medical school until an endowment of \$500,000 had been secured, and that women who desired to enter should receive their preliminary education somewhere else. Miss Mary E. Garrett, who had contributed most of the original Women's Medical Fund, completed the endowment on December 22, 1892, by a gift of \$306,977. Leading up to this gift there was a protracted three-sided discussion between Miss Garrett and her friends, the Medical Faculty and the Board of Trustees. The outlook for an agreement was often gloomy, and only one who was in a position to know, as I was, something of the ideas of all three parties to the negotiation, can realize on how many occasions the scheme came close to being abandoned. In this discussion, together with Welch and

Martin, Osler was deeply concerned. He had become very restive under the delay of the opening of the medical school, complained to me on one occasion of what he called the dry bones of post-graduate teaching, and even intimated that unless something were done he might be forced to go where there were some real medical students.

The decision as insisted upon by Miss Garrett, to fix permanently by the terms of the gift the conditions for admission to the medical school at an unprecedented standard, required no little courage, and although the results have abundantly justified it, it was then thought that it would greatly limit the number of students who would apply for admission. The first class of 17, including three women, entered in the fall of 1893. When, in the third year, they began to work in the hospital, first in the dispensary and then in the wards, Osler's genius as a medical teacher became more and more evident. He saw to it that the students came into the closest contact with the patients in the dispensary, and he organized the hospital wards so that the fourth-year students took an essential part in the management of the cases. Although this last had been the intention since the inception of the hospital, and the main

building had been designed to house 20 senior students, its practical application met with opposition and presented difficulties, and it was Osler's insistence that threw open the wards to the students, a fact, the thought of which, I think, always gives him pleasure.

He did, indeed, put the students into the wards, but he did not leave them there. He stayed with them, and if ever medical students got clinical instruction on a university basis, they did. It is not given to me to speak of Osler as a teacher, for my chapter ends with the beginning of the medical school. For me, and for others similarly situated, who had been reared in the expectation of the new order in medical education, the coming of Osler ushered in the complete realization of long-deferred hopes. He set for us a difficult goal, and helped and cheered us on the way by his wise precepts, his kindly, friendly commendation, his vigorous leadership, and more than all, by simply being himself.

It is no fault of his that the finished product is no better, but what good there is in me as a teacher and a physician I owe to him, and on this, his birthday, I lay it at his feet in grateful acknowledgment.

OSLER AS CHIEF OF A MEDICAL CLINIC

By LEWELLYS F. BARKER

Internal medicine, like other branches of science, though making at all times some progress, is subject in its advance to fits and starts, the result of unusual concatenations of events. The opening of the medical clinic at The Johns Hopkins Hospital in 1889 was an opportunity for helping on the science and art of medicine that might amount to either much or little, depending upon its seizure. The time corresponded to the flood-tide of natural science. Biology, physics and chemistry had participated in the great rise. Medicine, always quick to apply to its own service the results of investigations in the fundamental sciences, had responded by establishing a whole series of special medical sciences (anatomy, histology, embryology, physiology, physiological chemistry, pharmacology, pathological anatomy and physiology, bacteriology), to be studied and taught by men who gave up their lives exclusively to their promotion; these sciences were to serve as a foundation upon which a great superstructure of clinical science and art might be built. The place to be filled, the professorship of medicine in The Johns Hopkins University, which carried with it the appointment as physician-in-chief to The Johns Hopkins Hospital, was in several ways unique, at least as far as medicine in America was concerned. For, in the first place, according to the will of Johns Hopkins, the well-endowed hospital was designed to be an integral part of the medical school of an endowed university, and funds were provided for salaries for the leaders of the clinics as well as for the chiefs of other university departments, one of the circumstances that, combined with others, led to the abandonment of the hitherto-prevailing "proprietary medical schools" and to their replacement by medical schools organized as parts of great universities. In

the second place, The Johns Hopkins University, through the action of its trustees, and of its first president, Daniel C. Gilman, had been organized, in all its departments, in the interests of original research as well as of competent instruction; with distinguished investigators in the arts department and with men like Martin and Brooks in biology and physiology, Rowland in physics, Remsen in chemistry, and Welch in pathology, it was clear that capacity for personal research and the power to stimulate others to engage in fruitful researches were regarded, along with ability to teach and to organize, as essential requirements of the occupants of chairs in the university. And, in the third place, the trustees of the hospital, in consultation with the president of the university, the professor of pathology, and Dr. John S. Billings of the surgeon-general's library, had planned and built (out of income from the endowment), a hospital that, at the time of its completion, offered better facilities for the organization and conduct of clinical work than had heretofore been available in the United States. The ideals cherished in the university, the material equipment at the hospital, the opportunities and possible rewards open to the clinical leaders who might be appointed, combined to provide unparalleled places for occupancy. If, then, for these positions clinical men could be found, who, by native ability and experience, would measure up to the extraordinary time and the unusual opportunities, success in the highest sense for the new institution would seem to be ensured. The chair of medicine is, by common consent, the most important clinical chair in a university medical school. For this professorship the university faculty recommended, and the trustees confirmed, the appointment of

Dr. William Osler, then engaged in teaching medicine in the University of Pennsylvania and in consultation practice in Philadelphia. A member of a distinguished Canadian family, trained in medicine first in the University of Toronto and in McGill University in Montreal, and, later, as a graduate student, in the clinics and laboratories of England, France and Germany, interested and occupied in research and teaching in histology, physiology, pathology and parasitology as well as in internal medicine, and possessing personal qualities that even in youth marked him as a potential leader of men, the appointee entered upon his work with an enthusiasm that was stimulating, began to organize his department, selecting a group of young men as assistants, and soon set an example in practice, teaching and investigation that was contagious. The office and the man were suited to one another. The time, the place, and the person formed a happy conjuncture that was to mean much for internal medicine in America and in the world.

Of the set of brief contributions here published concerning Professor Osler's work in Baltimore, those dealing with his practice, his teaching, and his original inquiries are written by others; the part assigned to me is the preparation of a memorandum outlining the principles to which he, as the organizer of a medical clinic, persistently adhered, and the methods he employed in their practical application. He had very definite ideas of what a medical clinic should be and he felt keenly the responsibility of seeing to it that the functions of the clinic were faithfully performed. For him, the welfare of the patients who presented themselves in the clinic for diagnosis and treatment came first; next, came into consideration how undergraduate and graduate students could best be taught; and, finally, came solicitude that every opportunity for contributing to the advance of our knowledge of internal medicine should be eagerly seized. He took care to promote in every way possible the material, the scientific, and the moral interests of all who were associated with him in his work; his personal advantage concerned him but little, though to anyone who aimed at such objects and achieved such purposes as he did, a modicum of profit and a maximum of honor and prestige were bound to accrue. The principles he fixed upon and the methods he used to illustrate them were manifoldly derived. In part they grew out of personal practical experience, in part they had their origin in other clinics in this country and in Europe. Men who were familiar with clinical work and clinicians in the larger centers of America, those who had "walked the hospitals" of London and Edinburgh, those who knew the laboratories and the clinical institutes of Austria, Germany and Holland, and those who had visited the clinics conducted by the best internists in France, had no difficulty in recognizing the sources of certain of the features of the organization of the medical service in Baltimore. Professor Osler's clinic synthesized diverse elements into a harmonious whole; it represented a new form, good in itself for its time, and yet plastic enough to admit of remoulding at later need. The limits of this article will permit of only brief comment upon the plan of organization and upon the way it was managed.

Where activities are complex, be they those of a factory, of a business office, of a scientific laboratory, or of a medical or surgical clinic, organization and management are two executive functions that must be properly exercised, if the work is to be successful. Organization involves: (1) An investigation of the conditions that exist and of the requirements of the whole situation; (2) the planning of a scheme that will meet the requirements, that will effectively and systematically correlate the activities of the working force, the materials, the equipment and the working space, so that the functions of the institution shall be competently, speedily and economically performed; and (3) the actual installation of the system as planned. Management, or the art of conducting an establishment after its organization has been devised and initiated, involves: (1) The attainment of the results that are aimed at; (2) the overcoming of obstacles that are incident to the conditions under which the work has to be done; and (3) the application of knowledge and skill in the training of the staff, in the setting up and in the maintaining of standards, in the providing of suitable incentives, and in the establishing of right relationships between the leader and the led. The head of an institution, or of a department, who creates an organization that is adequate, and who manages it with skill, demonstrates his executive capacity.

On Professor Osler's appointment as physician-in-chief to The Johns Hopkins Hospital in 1888, he found certain conditions already existing that were to some extent determining, at least as far as the general organization of the institution was concerned. The buildings already completed included one for general administration, with a building on each side of it for private patients, a long row of public ward buildings behind, a building for a general out-patient department, a nurses' home, a pathological laboratory, a general kitchen and a laundry. In other words, a "general hospital," in which medical and surgical patients (free and pay) were to be received, distributed and treated, and in which, later on, medical students were to be taught, had been constructed on the pavilion system. There was no spatial concentration of the work of the single departments in separate institutes such as had already developed in some of the European centers, or, as was later adopted in the institutes built for psychiatry and pediatrics on the grounds of The Johns Hopkins Hospital; on the contrary, to pass from some of his private patients in Ward B at the southwest corner of the grounds to some of his public-ward patients at the northeast corner, the internist and his staff were compelled to walk through corridors that extended along two sides of a square containing 14 acres! As in most general hospitals, the functions of general superintendency, financing, accounting, nursing, purveying and housekeeping had been centralized, and with them the heads of the clinical departments had but little to do. But, thus relieved of much administrative detail, the head of the medical department, who was appointed permanently and had a continuous service, was to have a large degree of autonomy in the diagnosis and treatment of patients, in the selection of his staff, in the character and amount of his teaching, and in the conduct of research. His staff was to con-

sist (1) of younger men who lived in the hospital and gave their whole time to the department, and (2) of senior associates who lived outside, giving part of their time to the hospital and part to private practice. The chief of the medical service was to be paid a salary in order that he might make the work of the hospital and of the medical school his main occupation and interest, though he was permitted to supplement his income and clinical experience by private consultations. The activities of the different clinical departments were to be correlated partly by the general superintendent of the hospital, and partly by a medical advisory board that made recommendations to the trustees of the hospital. When Professor Osler arrived, the buildings, and the general plan of organization already completed, had to be accepted as they were: the plans of his department had to be drawn so as to fit into them.

It was fortunate that The Johns Hopkins Medical School was not opened until 1893 and that clinical instruction of undergraduates did not begin until 1895, for six years were thus available for perfecting the organization of the wards, the outpatient department, the laboratories, the staff, the records, the library, the hospital, the medical society, and the care of patients in the hospital before the function of teaching undergraduates was added. Courses for post-graduate students were, it is true, offered during this period, but the number of candidates was small and the work was not burdensome. With few patients at first, a small staff, and a limited amount of post-graduate instruction, leisure was given for making plans (and for modifying them after small-scale trials in executing them), for instituting standards, for writing a text-book that concisely embodied the principles and practice of medicine and that was destined to have an unprecedented distribution among physicians and students, and, in general, for establishing traditions of the better sort in the clinic. With the organization thus far planned and installed before the students of the medical school entered upon their clinical work, it was a relatively easy matter to expand it and to adapt it to the functions of undergraduate instruction when the time for this arrived.

When the definitive history of Professor Osler's work in Baltimore is written, many details of his analysis of the functions of the clinic, of his applications of the principle of division of labor in the clinic, of his methods of selecting men, of assigning them to appropriate tasks, and of motivating them to high endeavor, and of the personal qualities through which he exerted that profound and lasting influence upon patients, students, assistants, and colleagues for which he is so widely known, must be recorded. The scope of the present memorandum will permit mention of only a few of the more outstanding features of his organization and management, of those parts that made his clinic so successful a department of a university teaching hospital as it is known to have been.

One important element of success in the new clinic was the arrangement for a graded staff, particularly for a graded, whole-time, resident staff, among the members of which the responsibilities of the work were divided, not according to a so-called "military type," but rather in the manner of the

so-called "composite functional type" of organization. The professor of medicine (physician-in-chief to the hospital), though giving most of his time to the work of the clinic, lived outside the hospital, as did the associate professors who "visited" the wards, the out-patient department, and the laboratories. The resident physician, the assistant resident physicians, and the medical internes lived in the hospital and were in close contact with the work always by day and as far as was necessary also by night. The resident staff of the clinic consisted of two parts: (1) A lower resident staff constituted by the medical internes appointed for a single year, usually on graduation with high standing from the medical school; and (2) an upper resident staff made up of the resident physician and several assistant resident physicians, usually men of exceptional promise, men who had already served as hospital internes and who were willing to enter upon a more or less prolonged resident service, often of several years' duration, in order to secure the best possible training for the "higher walks" of internal medicine. This upper staff was chosen partly from the lower staff, partly, in order to prevent "inbreeding," from members of the resident staffs of hospitals in distant medical centers. The position of chief resident physician, which carried with it large responsibilities and opportunities, was a prize to be won only by men of exceptional ability, extensive experience, and favorable promise. Thus, those receiving it in Professor Osler's time, included Henry A. Lafleur (1889-1891), William S. Thayer (1891-1898), Thomas B. Fletcher (1898-1901), Thomas McCrae (1901-1904), and Rufus I. Cole (1904-1906). The careers of these men during their terms of service and since illustrate on the one hand the wisdom of him who selected them, and on the other the growth-promoting influence of the duties and authority attached to the office. The assistant residents, even those who did not later become chief resident physicians, often continued in office for several years. Such an upper resident staff, supported by internes and by senior students, besides forming a whole-time group of enthusiastic young internists for development under ideal conditions, afforded an excellent working force for carrying on the routine of the wards, laboratories, and out-patient department; this left the physician-in-chief and his visiting associates largely free for planning, standardizing, supervising and controlling the practice in the clinic, for teaching, and for promoting original inquiries. The historian bent on analyzing the conditions of achievement in Professor Osler's clinic will do well to consider carefully the significance of this upper resident staff.

A second characteristic feature of the medical clinic organized by Professor Osler was the introduction of more extensive and more systematic courses of instruction in the practical-technical methods of gathering data regarding disturbances of structure and function in the sick than had before been customary. The importance of careful history-taking and of accurate physical diagnosis had been, it is true, generally recognized; but the machinery of instruction in these forms of fact-accumulation had been inadequate in the majority of medical clinics, and one of the first tasks of the new clinic con-

sisted in planning and installing a better organization for this purpose, and in seeing to it that the example set by all who participated in the practical work of diagnosis in the clinic was consistent with the methodological teaching. The most distinctive advance made in instruction in technique was, however, the establishment of a systematic course in the application of the laboratory methods of chemistry, physics, and biology to the study of patients. Students in their third year of the medical school were not only taught the principles of these methods, but for two or three afternoons throughout the year were thoroughly drilled in the practical technique of these methods, so that, when the course had been completed, each student had attained to real skill in the use of all the more important ways of examining clinically the blood, the stomach juice, the feces, the urine, and the cerebrospinal fluid. No medical school has yet devised a perfect system of training, and the graduates of The Johns Hopkins Medical School, like those of other schools, doubtless exhibit certain special defects, but by common consent, they are well-trained in the methods of gathering clinical facts and especially in the technical procedures of the clinical laboratory. By many it is believed that, of the several contributions made by Professor Osler to the organization of the clinic, the development of the clinical laboratory and of the thorough education of students by competent instructors in clinical laboratory work before entering upon their duties in the medical wards is preponderant.

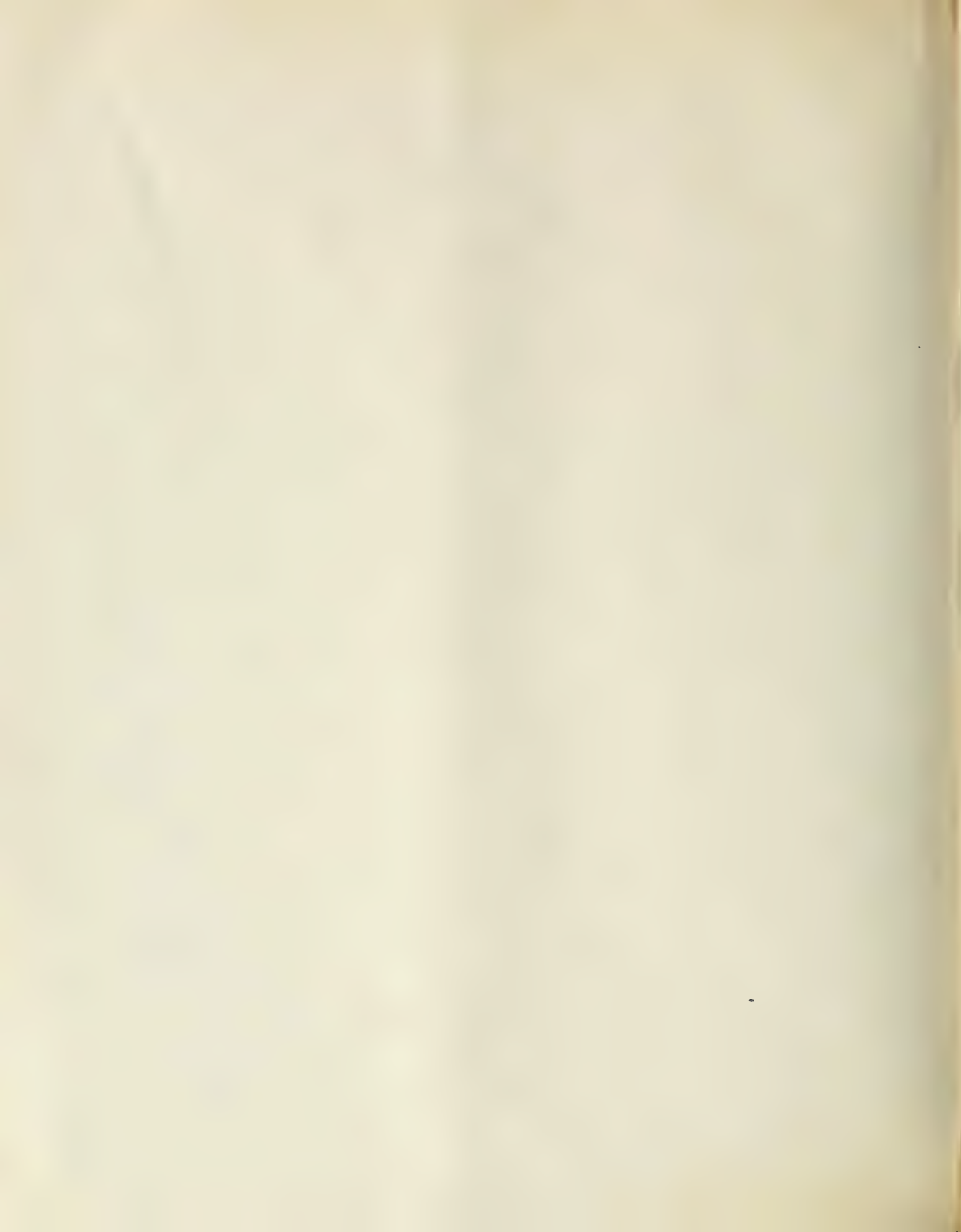
A third distinctive mark of the organization in Dr. Osler's clinic was the arrangement by which each student of the medical school became for a considerable period a member of the group that actually did the work of the diagnosis of disease and of the treatment of patients in the hospital. Thus each student in his third year, after having had instruction in history-taking and in the elements of physical diagnosis, assisted, under the supervision and control of instructors, in recording histories and in making physical examinations in the out-patient department. More important still, through the fourth year of the course, each third of the class acted successively for three months as "clinical clerks" in the stationary medical clinic, giving their whole time to the work of the medical wards. Thus the medical staff was reinforced during the entire school year by 30 student assistants, who, under the eye of the resident staff, took the histories of all new patients, assisted the internes in the making of the first physical examinations, made all the clinical laboratory tests on these patients, and accompanied their chief on morning rounds. At these rounds, the clinical clerk gave orally an epitome of the findings in the patient, watched the processes of control examinations used by the professor, and participated at the bedside in discussions of the pathological-physiological, pathological-anatomical, and etiological bearings of the case. He looked up recent articles on the subject and reported them at later ward rounds, followed the patient to the operating room if surgical procedures were indicated, watched the effects of the treatment employed in the case of each patient directly assigned to him, and kept in touch with him during conva-

lescence at his home after discharge from the hospital, or in the event of a fatal issue attended the autopsy and the pathological-clinical conference that followed it. The fact that through all this he was regarded as an integral part of the working group of the clinic, the knowledge that the anamneses he registered and the results of laboratory tests he made became a part of the permanent records of the hospital, the feeling of responsibility he had when he realized that the diagnosis made and the treatment instituted were based in part upon data accumulated by him, the personal relationships established between student and professor at the hospital and on delightful Saturday nights at the professor's home at 1 West Franklin Street—all this combined to make the time of the clinical clerkship in Professor Osler's clinic a period of rich experience and of intense stimulation, never to be forgotten by any pupil who passed through it. Even in the more formal teaching of the clinic, it was Professor Osler's custom to permit the clinical clerk to have a share. Thus, at the main teaching event of the week, the crowded Saturday clinic in the amphitheater, where all the students of the third and fourth year, the whole resident staff, many of the visiting physicians of the hospital, physicians of the town and medical men from a distance were assembled, the clinical clerk gave a part of the clinic; he was always asked to tell the audience briefly (and from memory unaided by notes) the main points of the anamnesis of the patient and was called upon from time to time throughout the hour to report on laboratory tests and X-ray findings, or to give his opinion of the significance of some datum. The pupil-teacher thus grew accustomed to facing a large audience and to thinking and speaking on his feet, an admirable preparation for some of the contingencies of later professional life. The student-assistantships in the out-patient department (in the third year) and the clinical-clerkships and all that they implied (in the fourth year) were, then, vital parts of the organization of The Johns Hopkins Medical Clinic.

Though the organization of the clinic in Baltimore presented, as we have seen, an interesting combination of novel features, no organization, no matter how well planned and installed, can function effectively without the skilful application of the art of management, and in the art of management the director of this clinic was to prove that he was a master. Thoroughly familiar himself with the principles, methods and problems of internal medicine, enthusiastic about, and for his time well trained in, the preclinical sciences that are fundamental, he possessed that personal experience in his subject and that superior ability that are always prerequisites to competence as a manager and to the command of the respect of those that are to be managed. He understood human nature and loved it, despite its faults and its frailties; no chief ever secured in greater measure the good-will and loyalty of his staff. Though he could be firm on occasion, he rarely found need to act as a strict disciplinarian. He was always cognizant of the good qualities of those about him, and though not blind to their defects he had learned that great lesson of successful management that, for most subordinates, a word of apprecia-



The Saint Johns Hopkins Hospital



tion is of far greater value as a stimulus to good work than a volume of carping criticism. He possessed to an extraordinary degree the capacity of making you feel that he was interested in you and in your personal welfare; to come into contact with him meant, for most, the birth of a genuine affection for him. He had an orderly mind and manner; he lauded punctuality in a doctor and was always punctual himself. He seemed never to be in a hurry and yet he wasted no time. Many a man recalling an interview that seemed leisurely when it occurred has been surprised, on analyzing it afterward, to find how brief it had been. He belonged to the first of the two groups—the “larks” and the “owls”—into which men have been playfully divided. He retired early and was an early riser. At one time he lived for some months in the hospital and it is asserted that men learned to set their watches at 10 p. m. by the sound of his boots as they dropped on the floor outside his door. His more important work was done in the morning hours; for him “great business must be wrought ere noon”; private consultations were relegated to the later hours of the day. His power immediately to grasp the significance of situations, his ability to make quick decisions, his unflinching tact and discretion, together with his wide sympathies and his lively sense of humor made it a pleasure to transact business with him. His ideals he kept ever before him and was ambitious to realize them, and these ideals and this ambition were alluring also to those whom he led. Much might be written, were there space, of the ways in which he overcame obstacles and met important emergencies, of the motives he appealed to when he desired to excite men to action or to

arrive at a decision, and, in general, of those traits of character that act “directly by presence, and without means,” or what is sometimes called “personal magnetism.” Many of the qualities that make for successful management, though easy enough to recognize when they exist, are difficult of analysis and perplexing to the understanding. Some men are able to secure control without contest; “whether they stand or walk or sit or whatever thing they do,” they can place men under their power. Of such character-control and of prestige-control Professor Osler had his full share. But, more important than these, he had grasped, as it were intuitively, the newer principles of association and of group organization. A man of many selves, he could enter into helpful association with many different groups, letting his mind interact with the other minds of each group for the purpose of arriving at ideas, feelings and impulses in common. More than most he had learned how to live with other men, to discuss without antagonism, to secure co-operation by the subtle psychic process of reciprocal penetration. In this lay the secret of his co-ordinating power. He knew not only how to bring the various activities of his clinic into proper relation with one another, but also how to link the clinic with other departments of the university, with the medical profession, with the public near and far, and with national and international associations of different kinds. Through his power as an organizer and as a manager Professor Osler might, then, have truthfully said, as did one of old, “I magnify mine office.” And it is precisely capacity for such magnification of office that, along with ability to plan and to direct, is a distinguishing criterium of the superior executive.

SOME OF THE EARLY MEDICAL WORK OF SIR WILLIAM OSLER

By W. T. COUNCILMAN

William Osler, the son of the Rev. F. L. Osler, was born in Tecumseh, Ontario, in 1849. He was one of a large family, and his ancestors were a vigorous, long-lived race. He graduated from Trinity College, Toronto, in 1868, began the study of medicine in the University of Toronto, and after two years went to McGill University, Montreal, where he received the M. D. degree in 1872. From 1872 to 1874 he studied abroad, working in the various London clinics, in the laboratory of University College, London, and in the laboratories and clinics of Berlin and Vienna. He came in contact with many eminent men, studied methods of work and of teaching, and the influence of this period of European study is seen in his after career. In 1873 he obtained the licentiate of the College of Physicians of London, in 1878 he was made a member of the college, and in 1884 was elected to the fellowship. In 1874 he returned to Montreal, was made lecturer on the institutes of medicine, and shortly afterwards was given the professorship. Under the institutes of medicine were comprised the courses in physiology and pathology, the latter limited to 20 lectures. At the end of 1874 he was made physician to the Small-pox Hospital, and in the following year, owing to the interest which he showed in comparative anatomy,

the professorship of helminthology, in the Veterinary School of the University, was taken into his already full hands. I shall discuss here only his early work, extending through the first four years of the Montreal period.

Beyond the bare facts, we know but little of his early education. In his various writings there are only scanty allusions to it save in the Toronto address, in which he mentions three men who were his early teachers and to whom he says he owes everything he has attained in life. These were the Rev. W. A. Johnson, of Weston, Ontario; Dr. James Bovell, of Trinity College, later professor of the institutes of medicine in Toronto University, and Prof. Robert Palmer Howard, of Montreal.

I have been able to learn but little of the Rev. W. A. Johnson, but it is evident that he was one of the many clergymen of the Church of England who have sought in various scientific pursuits a wider range of intellectual activity than is given by their profession.* I have gained this conception of the

*The Scottish Church has produced very few of these men, and they have been rare in America. However singular this may seem, the reasons are obvious. The clergy of the Church of England possessed a liberal education, and the taking of Orders

Reverend Johnson from two passages in the early writings of Dr. Osler. In the first article published by him (Canadian Diatomaceae, Canadian Naturalist, 1870) when he was a student in Toronto, he thanks him for assistance in the use of books and microscopical apparatus. In this article there is an admirable description of the structure, mode of division and propagation of the diatom, which is evidently based upon observation. The mode of motion of the organisms is discussed and he is inclined to accept the hypothesis advocated by Professor Schultze, of Bonn. At the close he gives a list of 105 diatoms which he had collected and classified, giving also the localities where they were found and their frequency. He must have been for a long time interested in the subject and the organisms were collected over an extensive area. He gives credit to Mr. Johnson for having given him several of the specimens. He refers also to another clergyman, the Rev. Mr. Reade, who had invented a prism by the use of which the shell markings could be studied to better advantage, and which was loaned to him by Professor Bovell. The article shows familiarity with the microscope and capacity to use literature. The second reference to Mr. Johnson I have found in an article 12 years later (On Canadian Fresh Water Polyzoa, Canadian Naturalist, 1882) which was read before the Natural History Society. There is here also an admirable description of the organisms with the differentiation of the species, but its main interest is in showing how early Osler—probably through the influence of Mr. Johnson—became interested in the study of nature. "In the summer of 1867, during a visit of my friend, the Rev. W. A. Johnson, of Weston, I showed him the masses (the gelatinous aggregates of the *Pectinatella magnifica* of Leidy) and we agreed to subject them to examination by the microscope, not having any idea as to their real nature. Judge of our delight when we found the whole surface of the jelly was composed of a collection of tiny animals of surpassing beauty, each of which thrust out to our view in the zoophyte trough a crescent-shaped crown of tentacles." A foot-note speaks of another clergyman, the Rev. Thomas Hincks, as the distinguished authority on British polyzoa.

His second teacher, Dr. James Bovell, seems to have been an interesting character. He was born in Barbados in 1817, went to England in 1834, studied at Guy's Hospital, and took the medical degree in Glasgow in 1838. He then went to

did not demand any extensive preparation for the examinations. Most of them had an assured living in pleasant country surroundings, and the dogma was simple, fixed, and did not admit of controversy. Proselyting was not actively pursued in the English church, and the souls of their simple parishioners were not a serious care. They must have found little intellectual stimulus in the society of the country squires, and many of them were perforce driven into the study of botany and other branches of natural science. The Scottish church, on the other hand, demanded long and arduous preparation for the ministry, and most of its members did not have the background of a liberal education. Like the Scottish character, the church was a fierce, aggressive force, its dogma logical and uncompromising, and its defence and extension involved a constant controversy, which left little time for the calm study of nature. In this country the conflicts of the sects give sufficient intellectual diversion.

Dublin, studied under Stokes and Graves for several years and after a severe attack of typhus fever, against the advice of his friends, who predicted a brilliant medical career, returned to Barbados. From there he went to Canada in 1848; took part in the establishment of the medical faculty of Trinity College, became Dean and Professor of the Institutes of Medicine, and also Professor of Natural Theology. After the disruption of this medical school he held a similar medical position in Toronto University. In 1870 he returned to the West Indies where he remained until his death. While there he took orders in the English Church and published a book on Natural Theology. He was regarded as an impractical, improvident man, was loved by his students and friends and took great delight in metaphysical discussions. Osler came under his influence in Trinity College, and in Toronto University, and he has dedicated to him the first pathological report of the Montreal General Hospital. It is not improbable that, through these two men and the atmosphere of his home, Osler acquired the interest in biblical and ecclesiastical literature which was such a prominent characteristic of his later life.

The third of these men was Dr. Robert Palmer Howard, professor of medicine in McGill University, whom Osler speaks of as his second father. He was a greatly respected teacher and practitioner of medicine and exerted a wide influence, but he was not a prolific writer.

While in London, Osler published two articles from the laboratory of University College. The first, "On the Action of Atropia, Physostigma, and Curare on the Colorless Blood Corpuscles," was read before the Royal Microscopical Society in 1873, and published in its journal. Such a paper as this was rather unusual at the meetings of the society which were mostly taken up with descriptions of microscopes, methods of preparation of microscopic objects, etc. The object of the investigation was to determine whether the antagonism between atropia and physostigma, which Fraser had shown to exist, could be demonstrated in the behavior of colorless corpuscles under the microscope, and the result was negative. It was interesting to find in the same volume with the paper of Dr. Osler a long, interesting and scathing review of Bastian's *Beginnings of Life* which had just appeared.

The second article, "An Account of Certain Organisms Found in the Liquor Sanguinis," was published in 1874, appearing in the Proceedings of the Royal Society. This forms one of the most important of Dr. Osler's contributions to medicine and demands a more detailed description in order to do justice to the originality shown in this article. From the massive literature on the subject four articles may be singled out, each of which was an important contribution to knowledge. In 1865, in the article of Max Schultze on the blood, certain bodies afterwards known as blood plates were for the first time adequately described; the second was the article by Osler, the third by Bizzozero in 1882, in which he gave a new method for their study and showed the part they played in thrombus formation, and the fourth by J. H. Wright in 1910, who demonstrated their histogenesis. The name blood plates, given to the bodies by Bizzozero, has been adopted.

It would be difficult to say who first saw and described them. At this period the fresh unstained blood was being actively examined by many with a view to the discovery of micro-organisms which might be the cause of infectious diseases. Zimmermann, in Rust's *Magazin f. d. gesammte Heilkunde* in 1846, and again in Virchow's *Archives*, Vol. 18, 1860, saw and described the bodies as small globules which he regarded as the elementary corpuscles from which the blood cells develop, but his description was very vague and he did not sharply separate them from other granules in the blood. The very remarkable article on the blood cells by Max Schultze conceals by its title "Ein Heizbare Objecttisch und seine Verwendung bei Untersuchungen des Blutes" (*Arch. f. Mikro. Anatomie*, Bd. I, 1865), the subject of the article much better than usually happens, in spite of the ingenuity which is often displayed in doing this. After a description of the varieties of the white corpuscles, the accuracy of which excites our admiration even now, he says "In the blood no constituent is without importance, and in conclusion I will call attention to a normal form constituent of the human blood which up to the present has been entirely neglected. I find in my blood and in the blood of numerous persons of different ages more or less abundant, irregular masses of colorless globules, the masses varying in size according to the number of globules which compose them. The globules themselves are from one to two micra in diameter and also occur separately in the blood. I have found three, four and even hundreds joined together, forming plaques of irregular size, 80 or more micra in diameter. These structures, on account of their irregular size and shape, give the impression of broken up tissue elements."*

This was the condition when young Osler was probably given the subject for investigation in the laboratory. He showed that these granular masses of Schultze were not present in the circulating blood, but were formed at the moment of examination by a rapid aggregation of the single bodies. He showed this by microscopic study of the blood, and also by the direct examination in salt solution of small clippings from the connective tissue of the rat in which he found the single bodies and not the masses of them, within the small blood vessels. He also showed that the conception of their presence in the blood in aggregations was untenable because the masses could not pass through the capillaries. He described the small bodies as exhibiting amœboid activity and saw filaments form in connection with them, which were probably fibrin. The article is admirable, clear and concisely expressed, with full literature references. The next reference to the blood plates is in an article "Infectious Endocarditis" (Seguin's *Arch.*, 1881), and here he anticipates Bizzozero's view of the part they play in thrombus formation. "In one case of mitral

stenosis a fresh vegetation when teased showed many closely packed spherules, some of which were larger than those met with in the ulcerative form. [These were the masses of micrococci.] I was greatly struck with the resemblance which certain of these bodies, in this instance, bore to the individual elements of Schultze's granular masses—those peculiar, granular clumps common in the blood of some animals and of impoverished* persons." In 1882 there appeared a further article, "Ueber den dritten Formbestandteil des Blutes," in the *Centralblatt f. d. med. Wissensch.*, No. 30, in which he emphasized the part they played in the formation of thrombi and a final article "On the Third Corpuscle of the Blood," *Medical News*, 1883, a rather popular presentation of the subject.

Osler returned to Montreal in 1874, bringing to his future work a remarkable equipment. He was 25 years old, possessed a vigorous healthy body, and a well-trained mind. His family was well and favorably known in the community, which gives no small advantage in a conservative society. He had received a valuable education, probably more valuable though different from that which men are now receiving. He had come into close contact with men of high ideals and good methods of work, he possessed the methods by which knowledge is obtained and had already made important contributions which gave him a reputation. He further had enthusiasm and the art of inspiring this in his students, native kindness of heart, a candid, open disposition, a great capacity not only for making friends, but for arousing the feeling of affection, and a fine sense of humor, never used to hurt, which made him a sought and delightful companion. He wrote well and easily, expressed himself simply and clearly, leaving no doubt as to the meaning, and the matter was well arranged. In spite of the number of these early articles, they all show care in preparation. He had also great capacity for work, and ambition, with a definite end in view. For such a man there are always opportunities waiting, and Osler found them in Montreal, as he would have found them anywhere, even with his friend Bovell in Nevis.

In the latter part of 1874, in addition to his position in the university, he was made physician to the Small-pox Hospital, which gave him opportunities for clinical study and an interest in the disease which he has always retained. With the salary which the position gave he purchased microscopes for teaching in the medical school. In 1876 he published in the *Canadian Medical and Surgical Journal* three articles on small-pox: (1) "The Initial Rashes of Small-pox"; (2) "On Hemorrhagic Small-pox"; (3) "A Form of Hemorrhagic Small-pox," which are valuable contributions to our knowledge of the disease. They show accurate observation, good clinical judgment and a marked power of differentiation of conditions both clinical and pathological. He had studied skin diseases with Tilbury Fox in England, and the influence of these studies is shown here. It was an important work for him, for

* I have quoted from this article for one reason because it was used as a reference in the course of physiology given by Newell Martin in 1878, and the plate when I opened the volume appeared as a familiar friend. No one appreciated more than did Doctor Osler the importance of familiarizing students with the original sources of knowledge, and this was always done in Martin's laboratory.

* Osler did not usually use such ambiguous expressions; the presence of such masses in the blood might be regarded as one of the disadvantages of economic poverty.

in the small-pox hospital he first acquired the power of close observation of skin lesions and the ability of differentiation and description which was afterwards such a marked feature in his clinical work.

A very interesting article appeared in the same journal in 1876, "On the Pathology of Miner's Lung." It is based upon the examination of the lungs of a coal-miner who died in the small-pox hospital, and in whom the condition was very marked, and several other cases showing various degrees of the same condition. It is a good piece of work, shows much originality, and is to be regarded as the best article in English on the disease, which was first described by Pearson in 1813. In this article for the first time the large mononuclear phagocytes were differentiated from the smaller corpuscles, and Osler showed that the large cells were those most actively concerned in the phagocytosis of the carbon. He says: "One most curious specimen was observed. On an elongated piece of carbon three cells were attached, one on either end and a third in the middle, so that the whole had a striking resemblance to a dumb-bell. I could hardly credit this at first, until by touching the top cover and causing the whole to roll over, I quite satisfied myself that the ends of the rods were completely embedded in the corpuscles and the middle portion entirely surrounded by another." His description of the position of the carbon in the lungs and its relation to the lymphatics is accurate. He gives a figure of a microscopic piece of coal which was found and which showed the scalariform tissue of ferns, thus proving its origin, and another piece with two holes representing the dotted cells of firwood. In conclusion, there is an experimental study of the effect of foreign bodies in the tissue made by the injection of india ink into the axillæ and lungs of kittens.

The study of the blood plates gave him a familiarity with blood examination which he utilized in the study of anæmia, and there are several papers on this in 1877. The first of these, "A Case of Progressive Pernicious Anæmia," was published in association with Dr. Gardner in the Canadian Medical and Surgical Journal. It is probable that Osler wrote the paper and was responsible for the blood examination, and the description of the autopsy, which showed the usual conditions found in the disease. It is a good type of medical paper, the descriptions of the blood and of the marrow changes are accurate, and the relation between the blood changes and the marrow, which had been described by Cohnheim in the same year, is confirmed. An abstract of this article, with detailed measurements of the various blood cells "Ueber die Beschaffenheit des Blutes und Knochenmarkes in d. progressiven perniciöser Anämie" was published in the *Centralblatt f. d. med. Wissensch.*, 1877, No. 15, and a second article in the same journal on the study of a second case. Another article on the same subject, in which he was associated with Dr. Bell, appeared in the Transactions of the Canadian Medical Association, and here he gives Addison the credit for having first recognized and described the disease under the name of idiopathic anæmia. There is a final article in the following year, "Entwicklung von Blutkörperchen im Knochenmark

bei perniciöser Anämie," *Centralblatt f. d. med. Wissensch.*, 1878, in which he confirms Neumann's results of the study of blood formation in the marrow.

During this period also he wrote a number of articles on comparative pathology, the first on "Vermineous Bronchitis in Dogs, with Description of a New Parasite" was published in the *Veterinarian*, London, 1877. He found this parasite in the bronchi in an epidemic among dogs in Montreal. He gives an accurate description of the parasite, and the points of differentiation. It has been accepted as an original description and credited to him, the name *Filaria osleri* being one of its synonyms. The only mistake he made was in classing the organism among the strongyli and not the filariæ, the main difference being that the strongylus is oviparous and the parasite described by him produces living embryos. The lobular pneumonia which he found, associated with the presence of the parasites in the bronchi, he referred to the inhalation of inflammatory products produced by them. The paper closes with a discussion of the mode of infection which he thought was by the direct inhalation of the dried embryos and it would have been more valuable had he subjected this theory to experimental test. There is also a paper on *Trichina spiralis* (*Canadian Journal of Medical Sciences*, 1876) which gives a good description of the disease and the life history of the organism, but which does not add anything new, and there are a number of other articles which appeared at intervals up to the time he left Montreal for Philadelphia. In the last article, "An Investigation Into the Pork Supply of Montreal," which was conducted in association with one of his students in the veterinary school, A. W. Clement, who was afterwards well known in the early days of the pathological laboratory of the Johns Hopkins, he speaks of having made 900 autopsies in Montreal, in four of which trichinæ were found.

There are two interesting addresses in the period. The first was to the graduating class in medicine in 1875. It was probably the habit of the faculty to place the burden of such an address upon the youngest member. Reading over this address, one is conscious that Osler had very little interest in it. Probably he looked over other addresses given on similar occasions and they must have been a very poor lot. He gives the usual good advice to the students, telling them to keep up their reading, to observe patients well, and even at this early period introduces Sir Thomas Browne, but he does not use him effectively. It seems by far the worst thing he ever published; there is no trace of humor in it, and no indication of the remarkable power he showed in his later addresses.

The second address is of a totally different character. It represents much more work and care in preparation, as though Osler had concluded that giving addresses was to be part of his future work and that they should be good. There are a number of quotations, many of them apt, the usual good advice to students, and some really inspiring sentiments, well expressed. For instance, "You will have moments when the way appears rugged, and the outlook dark, but never fear; others have succeeded in the face of the same difficulties, and with patience and perseverance you will do so too. Banish the future. Live

only for the hour and its allotted work. Think not of the amount to be accomplished, the difficulties to be overcome, or the end to be attained, but set earnestly at the little task at your elbow, letting that be sufficient for the day, for surely our plain duty is 'not to see what dimly lies at a distance, but to do what lies clearly at hand.' It is difficult to give a student better advice than this. Of the family physician he says "But while the soldier and the statesman win honor and fame, the family physician will draw to himself the love and gratitude of manifold hearts; he will have no enemies, martial or political; and his labors, if directed by a wise and prudent skill, will be for the welfare and benefit of all."

From 1872 to 1878 was a great period in medicine; it just preceded the bacteriological era in which the nature of infection was established; Pasteur had completed his studies on fermentation and the silk-worm disease and was in the midst of his revolutionary work on anthrax; Koch, an obscure country physician, was beginning his studies on bacteria and

developing the methods which made their scientific study possible; Virchow was at the height of his fame; Cohnheim and Weigert had begun in Breslau and in Leipzig their remarkable work; a new university in Strasburg had just been established which became famed through its products; physiology, in England and under Ludwig in Leipzig, had taken a new life; Lister in England was in the midst of the work which revolutionized surgery; the modern medical clinic was slowly being established, and medicine was becoming scientific, its procedures based upon knowledge and not conjecture; new ideals and methods in medical teaching were being everywhere introduced; America was feeling the enormous stimulus of the promise given in the establishment of The Johns Hopkins University. Osler was under the stimulus of all the new life. He could easily have become a great scientist, but he chose the path which led to the formation of the great clinician which he became; a worthy associate of the great men who have made English medicine famous.

OSLER AS A PATHOLOGIST

By WILLIAM G. MACCALLUM

The statement may be safely ventured that no clinician in English-speaking countries has had at his command such a wide and detailed knowledge of morbid anatomy as Osler. There may be different opinions as to the reasons for his greatness as a teacher, as a man among men and in other ways, but hardly more than one opinion as to the foundation of his greatness as a clinician.

In the two small volumes of Pathological Reports printed at the McGill University, in a complete collection of reprints of his papers beginning in 1877, and in the first edition of his Practice of Medicine, the development of his knowledge of pathological anatomy may be clearly traced. Throughout there is no diminution in his keen enthusiasm and little change in the character of his interests, but there is an extraordinary advance in the clarity of his ideas keeping pace with the discoveries of the European and other workers in the field of pathology.

During a period of more than 40 years—years that have witnessed the most phenomenal advances in medicine—his attention was very largely devoted to these studies which were constantly maintained as the basis of his more purely clinical work.

Osler's training lay not in chemistry—the growth of bacteriology found him a spectator and experimental methods seem to have had little attraction for him. Nor did he attempt any protracted researches in pathology for its own sake. Instead his interest was and has always been in the observation of rather gross and striking anatomical alterations usually on account of the symptoms which they produced and not with the aim of investigating their minute details or their ultimate causes. In all this he has shown himself critical and sane and quite unwilling to pursue what seemed a fantastic theory unless convinced by definite proofs. He was skeptical of the

malarial organisms of Laveran for a time until he became familiar with them himself and demonstrated them in this country. He would not believe that the micrococci found in acute endocarditis were anything more than accidental invaders until he had convinced himself by actual studies of the valves.

But in his early days he did not wait for others to unearth new facts. He pressed ahead alone in the investigation of unexplained phenomena and was perhaps the first to see clearly the blood platelet which he described in 1874 as the third corpuscle of the blood.

He was early in the field with his studies of the bone-marrow in pernicious anemia and evidently recognized megaloblasts and other cells at a time when such recognition must have been very difficult.

But from the beginning he appears to have been more readily interested in the physical aspects of morbid anatomy, especially in so far as there could be traced a chain of events. In the first volume of the McGill reports he describes a case of idiopathic hypertrophy of the heart, the topography and effects of various aneurysms, cases of phthisis, pneumonia, cancer, ulcer of the duodenum, typhoid fever with perforation, incarceration of the ileum, etc. In the second volume is found a series of similar miscellaneous cases. Some of these were remarkable as, for example, the instance of aneurysm of the hepatic artery. It is to be noted that even in his discussion of these cases he showed that the special literature of foreign countries was quite at his command. He met with a case of hypertrophic cirrhosis of the liver—the first in his experience—and while he was studying it there appeared Hanot's thesis, the importance of which in relation to his own case he recognized at once. From this period at McGill University where he performed a great many postmortem examinations

and supervised them in the hands of students he acquired much of his familiarity with morbid anatomy. It is his spirit of serious research which has remained to inspire the splendid work in pathology carried on ever since in that school and his preparations formed the foundation of their magnificent museum of pathological anatomy.

Osler was impressed from the beginning with the usefulness of considering together a group or series of similar cases. There is something statistical about this plan, but since no two cases of any disease are precisely alike in all details, much light comes from the study of a series. This method may be traced through the work of his later years and in that of all of his pupils. It is apparent in all the papers of his Philadelphia and Baltimore periods and reveals his careful method of preserving minute notes on all he saw, for some of the recent studies refer back to cases encountered in the Montreal days.

Comprehensive papers on endocarditis, tuberculous pleurisy, peritonitis, pericarditis and abdominal tumors, followed and later similar analyses of long series of cases of typhoid fever, meningitis, erythema multiforme, Addison's disease, myxœdema, splenic anæmia, malaria and many other conditions. In these there is a sustained and constant interest in the pathological anatomical changes, but rather in their relation to the general history and symptomatology of the disease than for their own sake. The details of the causes and development of the lesions are discussed only briefly, but an important outcome of such studies was in several instances the more definite outlining of disease entities from the recognition of the repeated occurrence of the same group of symptoms and pathological alterations.

This has long been the first great step in the study of disease and it is for this reason that many of the great names in medicine are associated with the diseases in which they have been the first to discern the constancy of the association of several features. The ability to see these relations and to connect a group of phenomena with a common cause is given to few. It is only less difficult than to discover the hidden cause of disease.

On the other hand, with diseases well recognized by everyone, Osler's interest in new manifestations and new combinations of symptoms or lesions has been unflagging. After the long period of observation and study of typhoid fever in which he associated with himself all the men on his staff he analyzed

the disease from every point of view. However, in these studies only the grosser anatomical changes are considered and there was no special advance in the knowledge of the bacteriology or immunity reactions of the disease.

Syphilis has always claimed much of his attention and interest, although he has written little on it except in the form of text-book articles and papers concerning aneurysms. Nevertheless, the multifarious manifestations of this disease have formed a prominent subject in his teaching and he believed that there was much in the statement that he who knew all of syphilis knew nearly all of medicine.

In his later years he worked no longer at actual dissections and no longer studied the details of pathological anatomy with the microscope, but he never slipped into that state of confidence in unaided clinical diagnosis which would allow him to remain away from the autopsy room. Instead he came there not only to follow minutely the dissection of cases from his own hospital service, but to learn what he could from those belonging to the surgical and other services. His presence was an inspiration that led us to great efforts toward careful work, and his long experience and unflagging memory, which enabled him to recall the conditions found in a whole series of similar cases, gave us a background upon which the case under investigation stood out.

The pathological anatomy of his text-book is of this quality and it is for that reason that the students in pathology are told to read it. No one has written more systematically, or more concisely of the changes underlying the manifestations of disease; no one has recognized more clearly the boundary line between the known and the unknown or sifted more judiciously and unerringly the truth from error. His long habit of considering each disease on the basis of knowledge gained from the analysis of a large series of cases has allowed him to estimate justly the relative frequency and importance of each feature and to state them in the most helpful and orderly sequence. This clearness of vision with regard to the actual natural history of disease, always referring to a well-remembered series of cases, helped to make his teaching a memorable delight to his students. His actual contributions to our knowledge of pathology are many and important, but even more valuable to the science of medicine in general is his example, in that he has built his clinical medicine solidly on a foundation of pathological anatomy.

OSLER, THE TEACHER

By W. S. THAYER

Observe, record, tabulate, communicate.

Use your five senses. The art of the practice of medicine is to be learned only by experience; 'tis not an inheritance; it cannot be revealed. Learn to see, learn to hear, learn to feel, learn to smell, and know that by practice alone can you become expert. Medicine is learned by the bedside and not in the classroom. Let not your conceptions of the manifestations of disease come from words heard in the lecture room or read from the book. See, and then reason and compare and control.

But see first. No two eyes see the same thing. No two mirrors give forth the same reflection. Let the word be your slave and not your master.

Live in the ward. Do not waste the hours of daylight in listening to that which you may read by night. But when you have seen, read. And when you can, read the original descriptions of the masters who, with crude methods of study, saw so clearly.

Record that which you have seen; make a note at the time;

do not wait. "The flighty purpose never is o'ertook, unless the deed go with it."

Memory plays strange pranks with facts. The rocks and fissures and gullies of the mountain-side melt quickly into the smooth, blue outlines of the distant panorama. Viewed through the perspective of memory, an unrecorded observation, the vital details long since lost, easily changes its countenance and sinks obediently into the frame fashioned by the fancy of the moment.

Always note and record the unusual. Keep and compare your observations. Communicate or publish short notes on anything that is striking or new. Do not waste your time in compilations, but when your observations are sufficient, do not let them die with you. Study them, tabulate them, seek the points of contact which may reveal the underlying law. Some things can be learned only by statistical comparison. If you have the good fortune to command a large clinic, remember that one of your chief duties is the tabulation and analysis of the carefully recorded experience.

The collection and study of your own observations is much, but he who works in his own small compartment leads, after all, a restricted and circumscribed life. Go out among your fellows, and learn of them. The good observer is not limited to the large hospital. The modest country doctor may furnish you the vital link in your chain, and the simple rural practitioner is often a very wise man.

Respect your colleagues. Know that there is no more high-minded body of men than the medical profession. Do not judge your confrères by the reports of patients, well meaning, perhaps, but often strangely and sadly misrepresenting. Never let your tongue say a slighting word of a colleague. It is not for you to judge. Let not your ear hear the sound of your voice raised in unkind criticism or ridicule or condemnation of a brother physician. If you do, you can never again meet that man face to face. Wait. Try to believe the best. Time will generally show that the words you might have spoken would have been unjust, would have injured a good man, and lost you a friend, and then—silence is a powerful weapon.

When you have made and recorded the unusual or original observation, or when you have accomplished a piece of research in laboratory or ward, do not be satisfied with a verbal communication at a medical society. Publish it. Place it on permanent record as a short, concise note. Such communications are always of value.

Mix with your colleagues; learn to know them. But in your relations with the profession and with the public, in everything that pertains to medicine, consider the virtues of taciturnity. Look out. Speak only when you have something to say. Commit yourself only when you can and must. And when you speak, assert only that of which you know. Beware of words—they are dangerous things. They change color like the chameleon, and they return like a boomerang. Do you know the story of the young physician, about to enter practice, who was sent by his father to his old friend, Sir William Stokes, for advice? A pleasant conversation, and, at the door—

way, a last word: "Charley, don't say too much." Then, at the gate, a voice: "Charley, come back a minute; I'm very fond of you, my boy; don't do too much."

"Don't do too much." Remember how much you do not know. Do not pour strange medicines into your patients. Our greatest assistance is given by simple physical and mental means, and by the careful employment of such drugs as have been adequately studied, with regard to the action of which we have real information. Do not rashly use every new product of which the peripatetic siren sings. Consider what surprising reactions may occur in the laboratory from the careless mixing of unknown substances. Be as considerate of your patient and yourself as you are of the test-tube.

Familiarize yourself with the work of others and never fail to give credit to the precursor. Let every student have full recognition for his work. Never hide the work of others under your own name. Should your assistant make an important observation, let him publish it. Through your students and your disciples will come your greatest honor.

Be prompt at your appointments; that is always possible. Many are always late at a consultation; few miss a train. There is no excuse for tardiness.

Live a simple and a temperate life, that you may give all your powers to your profession. Medicine is a jealous mistress; she will be satisfied with no less.

Save the fleeting minute; do not stop by the way. Learn gracefully to dodge the bore. Strike first and quickly, and before he has recovered from the blow, be gone; 'tis the only way. . . .

If you can practice consistently all this, . . . and then, if you can bring into corridor and ward a light, springing step, a kindly glance, a bright word to every one you meet, arm passed within arm or thrown over the shoulder of the happy student or colleague; a quick, droll, epigrammatic question, observation or appellation that puts the patient at his ease or brings a pleased blush to the face of the nurse; an apprehension that grasps in a minute the kernel of the situation, and a memory teeming with instances and examples that throw light on the question; an unusual power of succinct statement and picturesque expression, exercised quietly, modestly and wholly without sensation; if you can bring into the lecture room an air of perfect simplicity and directness, and, behind it all, have an every-ready store of the most apt and sometimes surprising interjections that so light up and emphasize that which you are setting forth that no one in the room can forget it; if you can enter the sick-room with a song and an epigram, an air of gaiety, an atmosphere that lifts the invalid instantly out of his ills, that produces in the waiting hypochondriac so pleasing a confusion of thought that the written list of questions and complaints, carefully compiled and treasured for the moment of the visit, is almost invariably forgotten; if the joy of your visit can make half a ward forget the symptoms that it *fancied* were important, until you are gone; if you can truly love your fellow, and, having said evil of no man, be loved by all; if you can select a wife with a heart as big as your own.

whose generous welcome makes your tea-table a Mecca; . . . if you can do all this, you may begin to be to others the teacher that "the chief" is to us!

An eye whose magic wakes the hidden springs
Of slumbering fancy in the weary mind,
A tongue that dances with the ready word
That like an arrow seeks its chosen goal,
And piercing all the barriers of care,
Opens the way to warming rays of hope.
A presence like the freshening breeze that as

It passes, sweeps the poisoned cloud aside.
An ear that 'mid the discords of the day
Swings to the basic harmonies of life.
A heart whose alchemy transforms the dross
Of dull suspicion to the gold of love.
A spirit like the fragrance of some flower
That lingers round the spot that this has graced,
To tell us that although the rose be plucked
And spread its perfume throughout distant halls,
The vestige of its sweetness quickens still
The conscience of the precinct where it bloomed.

OSLER AND THE STUDENT

By THOMAS R. BROWN

In a lay sermon delivered before the Yale students a few years ago in which Dr. Osler offered them "A way of life"—"a path in which the wayfaring man cannot err, a life in day-tight compartments, the main business of which is not to see dimly at a distance, but to do what lies clearly at hand," and which had been the starting point of his life-habit—he began with two words which show more plainly than many pages could his real relation to the student—for these two words were "fellow students." In these words lay the real reason for his unique and lasting influence upon all who studied with him, for he, with his vast experience, his wonderful insight, his profound knowledge, his poetic vision, his deep sympathy, was still always at heart the student, always studying, always delving more deeply into the mysteries of health and of disease, giving always, yet always ready to receive, teaching, yet ever ready to learn.

To those privileged to be his students in the early days of the medical school—a truly golden age to each and every one of the small, though ever growing group, he preached, as he lived, a glorious philosophy of life, a joy in work, doing the day's tasks, "living for the day and for the day's work," with a wonderful belief in his fellowmen, never losing faith because some had failed him, giving without stint his best to everyone with no thought that some might prove unworthy of the trust. He felt with Goethe that "the classical is health, and the romantic disease," and he strove for the one with the Greek love of perfection, while for the other he had the passion of the truly adventurous spirit sailing on uncharted seas. To us who were his students in the early days of The Johns Hopkins Medical School, his memory is so vivid, so fresh, that it seems but as of yesterday when he worked and played in our midst, and we have but to close our eyes to see him in fancy, almost as clearly as we saw him in fact in the late 90's, the great teacher and the great student in his manifold relations to his students. Now we see him riding to the hospital in the Monument Street car, and to the group about him prophesying with keen yet ever kindly vision the ills—physical, mental and spiritual of the derelicts en route to the dispensary; here in the wards demonstrating the complex psychology of Gilles de la Tourette's disease, as exemplified by a poor bit of sodden humanity whose coprolalia but exemplified—in a way a bit embarrassing at times it is true—the symptom-complex he was discussing, or in an alcove off the ward playing with little

Theophilia as she was emerging from the night of cretinism into the day of normal happy childhood under his skillful guidance; now in the class-room of the dispensary—for he loved the polyclinic, and believed in its wonderful potentiality as a teaching factor—with one deft touch solving a case of great complexity, or bringing from his vast storehouse of knowledge the one last link needed in a disease-picture hitherto poorly understood, listening, suggesting, directing, teaching, guiding both student and patient, and all the while filling countless scraps of paper with the names of one of the three great teachers of his youth; now in the clinical laboratory studying a blood specimen, and suggesting to the student some line of original investigation which might, perhaps, light into flame the dormant investigator and research worker; now in the autopsy room studying in death the puzzles that he had helped to unravel during life; now walking through the wards and corridors of the hospital with a smile or an epigram for every doctor and nurse who passed, a kindly word, and his ever-stimulating psychotherapy—encouragement, optimism, hope—to every patient he saw; in his myriad activities always making each student feel that he also was but a student of health and of disease, of men and of morals, and yet such a student as to fire our minds, our souls and our bodies to renewed efforts so that we might, in some measure at least, prove worthy of this fraternity. To us who were privileged to be his students—his fellow students in those days, he was—and still is—always our inspiration and always our model. In him the fire burned so brightly that no dross nor tinsel could survive its pure flame, and he was ever "our cloud by day, our pillar of fire by night." With Bossuet he taught that "le bon sens est le génie de l'humanité," and he gave to us "a golden age which never rusts, a spring which never fades, eternal youth." Always true to himself and to others, he made us think daily of words of his beloved Plato "Whence has the progress of cities and nations arisen if not from remarkable individuals coming into the world we know not how and from causes over which we have no control?"

Is not the greatest tragedy of growing older the loss of our illusions—the discovery sooner or later that so many of the gods of our youth, Jove-like Olympians of those days when our world was young and pregnant with possibilities, have, after all, but feet of clay? But with "the chief" this could

never be. The more we learned, the more wonderful his boundless knowledge seemed; the wider our vision, the more limitless his appeared.

Everyone who has ever been his student is, as it were, still studying with him, or peripatetically following his footsteps as he journeys through life, always teaching some new lesson of medicine or of living. Every honor that has befallen him has enriched us and made us prouder of our brotherhood; every step upward or onward of his has made our paths easier and

the heights seem not so far away. We have rejoiced in his happiness and in his honors, and perhaps he has been helped in his sorrows by the knowledge that they are ours as well, for he has shown us how work could be made play, and how the real could be made ideal. Because of him our lives have been better, our successes more real, our failures less hard to bear, for through the tangled skein that spells life each of us knows that in him he has, and will always have, a teacher, a friend, and a true fellow student to the end of the chapter.

OSLER AND PATIENT

By THOMAS McCRAE

In all the relations of physician to patients there are two sides—the strictly medical and the personal. Some have a blind spot for the latter, but taking the profession as a whole these are in the minority. No one could work in close association with Sir William Osler without realizing that both sides were well developed in him. There was always the desire to do the best for the patient in a medical way, but the personal aspect was never forgotten. Patients were patients and not cases. Interest in the personal side was much in evidence and it was the exception for his patients to fail in appreciating this. There was always a great charity for the weakness of human nature and there were neither unkind nor hasty judgments. We know how often in his addresses he has emphasized the importance of this quality.

To the writer was given the opportunity of knowing the relation of Sir William Osler to the patient both by personal experience and by the observation of others. The former came by my having an attack of typhoid fever while a house officer in The Johns Hopkins Hospital. After the passage of years it is difficult to estimate in detail one's feelings towards his physician, but the main impression left on my mind after a long interval is that of absolute confidence. His visits were usually short, but when he had gone there was a feeling that everything was all right. The visit was nearly always marked by some cheering saying or amusing quip.

One incident comes to memory with regard to the impression made by him on a patient many years ago; it is also an example of curious coincidence. Back in the eighties one of my father's friends was stricken with a malady of which I heard some of the details discussed without realizing that they were to be remembered. The patient had Addison's disease with an unusual degree of pigmentation which attracted great

attention and was naturally commented on by his friends. I remembered hearing that he had gone to the United States to consult a physician and had come back realizing that he could not recover. These matters had apparently been completely forgotten, but were recalled when 25 years later the friend who

accompanied the patient on the journey said to me: "I wonder if you could help me to identify the physician whom Mr. X consulted in Philadelphia. His name made little impression on me at the time." This seemed rather a difficult undertaking, but I asked what he remembered of the visit. He gave the following details: "The examination was very thorough; he stripped Mr. X and went over him from head to foot. He said very little. (At this point the thought of Sir William came to my mind.) When Mr. X asked him as to the outlook, he said, 'Do you think you have enough of the grace of God to make a clergyman,' or something like that. At any rate Mr. X understood the meaning which was intended and commented with approval on the way in which it was conveyed." Afterwards I asked Sir William if he was the physician, and found that he was and that he remembered the patient very well.

This brings up another of his characteristics with regard to patients—the marvellous memory which he has of the details regarding many of them. On one occasion a physician brought a patient to consult him. The physician began to give the history when Sir William said: "I saw Mr. — before with so and so"—mentioning the diagnosis. Both the physician and the patient denied this until Sir William showed them the notes of the previous visit. It seems almost impossible to imagine that both should have forgotten the consultation, but such was the case. On many occasions patients came back to the clinic after an interval of years and Sir William could give the details of the history at once.



In one of his essays, which gives the title to a book, "Aequanimitas," he dwells on the importance of not permitting one's poise to be disturbed or allowing the expression to show what would be better concealed. He practised this in his daily work and many who came in contact with him never realized how much anxiety he often felt, but rarely displayed over patients. This was particularly true if it was a case in which a diagnosis had not been made and in which, therefore, the best treatment was a question of doubt. One such instance comes to mind of a young man with typhoid fever and severe hemorrhages. In this case, of course, we were suspicious of perforation. Sir William made a special trip to the hospital at my request to try and settle this point. The decision was that there was no positive evidence of perforation and exploration was delayed, but the signs of general peritonitis next day showed our error. I remember well his words on the fallibility of human judgment and of the sorrow that one felt when he had judged wrongly.

His influence over patients was marked and especially over those unfortunates whose nervous systems had suffered. As a general rule he did not spend a great deal of time over them in the hospital. However, the results came; in many cases no doubt, largely by faith in him. It has been said by some that Sir William was not particularly interested in psychotherapy, but one might say that he did not need to be—he practised it, not always consciously, perhaps, but always effectively. He had extraordinary patience with querulous patients and it was very rarely that he ever became irritated with them. With the patient who was ready to fight and be disagreeable he never argued: "Glad to see you come and glad to see you go" was a favorite answer.

Many interviews with patients come to memory. In one the center of the stage was occupied by a nervous woman, to whom something had been said in a very kindly way of the need of self-control. With the tears flowing freely and a handkerchief in active use she said: "Oh, Dr. Osler you misjudge me cruelly." He, standing at the foot of her bed, replied with a serious tone to his voice and a twinkle in his eye: "Madam, I learned early in life never to *judge* any woman and that rule I have strictly kept. Therefore, I cannot have *misjudged* you. Good morning"—and he was away before she could frame a reply. Later in the day the brunt of his hasty exit fell on me.

In a large private ward service it was not possible for him to spend a long time with each patient. To his house officers it was always a source of interest and a good lesson to observe

how he could get into and out of a patient's room without giving a chance for the flood-gates of talk to open. Many patients would lament that they had not been able to tell him this or that. But with this he had a remarkable ability in discerning when the patient needed a special interview and he was always ready to give it.

There was one subject on which he would never listen to a patient, and that was when something was said which reflected on another physician. When the patient began any such statements he showed his displeasure at once and if this was not enough a very sharp rebuke followed. In fact this was about the only thing which made him lose patience and was the rare occasion of his showing sternness. The talkative patient was a trial to him—and of whom is this not true? He used to have a very characteristic look when he escaped and I can remember his delight, after a particularly trying interview of the kind, when I quoted to him from "Kim": "The husbands of the talkative will have a great reward hereafter." However, he was rarely caught twice by the same person.

Of one class of his patients a word may be said—the doctors. He was consulted by many of the profession and especially in the latter years in Baltimore. This had grown to be a heavy burden, but one which he carried willingly. He never spared himself or thought of his own convenience when something was to be done for a physician or a member of a physician's family.

Of the attitude of patients towards Sir William much might be said. Perhaps the most striking characteristic was absolute confidence. There was the certainty that there would be no failure from lack of skill or interest on his part. His cheerfulness had much to do with this and the ability to give the desire to fight to those who had lost courage and hope. He was always careful in giving an opinion to put matters simply, so that the chance of misunderstanding would be as slight as possible. In the consideration of what a patient should do he always had in mind what he could do. It was a good lesson to observe the care which he took to avoid saying anything in the hearing of a patient which might cause disturbance or increase anxiety. This was especially marked when the outlook was being discussed and seemed unfavorable. He never forgot to be sure that the patient was not within hearing. In all the giving of advice he was sparing of words and might be described as one of those "who have not the infirmity, but the virtue of taciturnity, and speak not out of the abundance, but the well-weighed thoughts of their hearts."

OSLER AND THE TUBERCULOSIS WORK OF THE HOSPITAL

By LOUIS HAMMAN

Dr. Osler's interests were so universal that I fear I run grave risk of contradiction in saying that he showed a particular interest in tuberculosis. I came in contact very intimately with his enthusiasm for tuberculosis study and perhaps for this reason I exaggerate the position it held for him. Certainly

he never tired of reiterating to students the importance of a thorough knowledge of the two great infectious diseases, tuberculosis and syphilis. From the beginning of his career as physician-in-chief to this hospital he studied the tuberculous patients with minute care. The first patient admitted to his

medical service on May 16, 1889, was suffering from tuberculous peritonitis and one of the first clinical papers he published was upon this aspect of tuberculous disease. In 1903 I undertook at his request a study of all the cases of serous membrane tuberculosis that had been in the hospital up to that date and I noted that many of the histories have copious notes dictated by him.

That this interest in tuberculosis extended beyond the details of clinical observation is shown by the establishment in 1898 of a special fund for the study of tuberculosis, the initiative for its inauguration and much of the money coming from Dr. Osler himself. Dr. Charles D. Parfitt was appointed to conduct the work and a laboratory was equipped to afford him suitable opportunity for investigation. Unfortunately after an active year, which gave promise of substantial contributions to the study of tuberculosis, Dr. Parfitt was taken ill and the work was abandoned to be resumed some years later in the laboratory of the Phipps dispensary.

A further evidence of Dr. Osler's unflinching interest in tuberculosis, and his zeal for the dissemination of tuberculosis knowledge amongst the students, is the foundation of the Laennec Society in 1900. This was the first society in this country and, as far as I know, the first in the world to devote itself to the study of tuberculosis. I remember clearly the first meeting of the society held in the fall of 1900 in the basement under Ward G. Dr. Osler presided, outlining the aims of the society and explaining the appropriateness of its name; a review of Laennec's life and work followed. Since this date the society has continued to hold regular meetings and it has proved itself an important and stimulating center of tuberculosis interest in the hospital. Unfortunately, there are no records of the early meetings of the society, but I remember Dr. Osler's unflinching attendance at all the meetings and his brilliant and stimulating discussions.

Shortly after the establishment of the Laennec Society Dr. Osler with his peculiar prescience of coming events inaugurated the home visiting of tuberculous patients registering in the dispensary. At first this work was undertaken by medical students, Blanche N. Epler, Adelaide Dutcher and Elizabeth H. Blauvelt successively giving it their service. The study of Miss Dutcher reported before the Laennec Society and published in *The Philadelphia Medical Journal*, December 1, 1900, is, I believe, the first contribution in this country to lay the proper emphasis upon the importance of the home in the spread of tuberculosis. From this modest beginning grew the subsequent study and care and supervision of tuberculous patients in the dispensary. Dr. Osler soon enlisted the interest of Mr. Victor Bloede in the work and through his generous support a nurse was employed to visit and instruct patients in their homes. At the same time under his guidance the first steps were taken towards establishing a special clinic for the tuberculous. Although no separate rooms were available for this purpose, all tuberculous patients were put under the care of Dr. Herman Bruelle for detailed study and advice.

It would give a very incomplete impression of Dr. Osler's tuberculosis interests to omit reference to his activities outside

of the hospital. He was always deeply concerned about the social applications of medical knowledge and he played a prominent part in furthering and directing the awakening interest in the control of tuberculosis as a disease of the masses. For instance, he took a very active interest in the Tuberculosis Exposition held in January, 1904, under the auspices of the State Board of Health, the first exposition of the kind held in this country. Under his influence a remarkable collection of books on tuberculosis were displayed, illustrating the development of our knowledge of the disease from Hippocrates to modern times. Before the collection was dispersed Dr. Osler reviewed it with the medical students, illuminating each epoch with his surprising knowledge of the historical aspects of the subject.

In 1903 Mr. Henry Phipps learned of the work Dr. Osler was trying to do with such modest equipment and generously sent \$10,000 to support his endeavors. The check came quite unexpectedly and was the means for Dr. Osler to plan at once to materialize one of his dreams. With great enthusiasm he began to develop a special department for the study of tuberculosis and the care of tuberculous patients. Mr. Phipps' additional gift of over \$20,000 made it possible to remodel the old stable standing between the dispensary and pathological department buildings into a two-story structure with four rooms on each floor. The building was formally opened at a special meeting of the Laennec Society on February 21, 1905, and the first patients were received on the first of March of the same year.

Dr. Osler left the hospital the year the tuberculosis dispensary was opened, but his interest in the department never ceased. Messages of encouragement and appreciation came at irregular intervals. Whenever an article appeared by a member of the staff, usually the first and always the dearest recognition was a postal or a brief note dashed off in his characteristic way. As the dispensary gradually grew into a recognized place in the medical clinic, at every turn of fortune there came his cheering congratulation. It is impossible for me to look back upon those years without the deepest emotion. I do not know if Dr. Osler ever appreciated what these crisp, kindly messages flashed from abroad really meant for us, nor am I able adequately to express all we felt. Certainly this much is true, they were always the brightest ray of encouragement to our work, the most comforting reward that made us forget the long dreary hours of labor and the discouragement and doubt that often assailed us.

Since the first few years the tuberculosis dispensary has grown steadily in importance. Further gifts from Mr. Phipps allowed the hospital to add to the building in 1908, doubling its capacity. Recently the generosity of Mr. Kenneth Dows has further improved the building and has put the research department of the dispensary upon a sound footing. The tuberculosis clinic is a very different department now from the modest dispensary arrangements of a physician without a room to work in and with no other equipment but his stethoscope. But this is the fruit that has grown from that tiny seed of interest and enthusiasm planted by Dr. Osler many years ago.

INFLUENCE ON THE RELATION OF MEDICINE IN CANADA AND THE UNITED STATES

By THOMAS B. FUTCHER

Sir William Osler has done more than any other member of our profession to bring about cordial and intimate relationships between its members in the United States and Canada. A Canadian by birth, a graduate of McGill University, Canada's most distinguished medical representative, and a man with a most magnetic personality and great breadth of sympathies and interests, it is only natural that he should have exerted a most potent influence in encouraging close associations between the members of the profession in the two countries. Particularly was this the case after his call to Philadelphia in 1884, and to Baltimore in 1889. While this bond has naturally been more intimate between internists, his influence indirectly brought about a closer contact between the members of the other specialties.

Although Osler was graduated in medicine from McGill University, he was born at Tecumseh, Ontario, on July 12, 1849, and was educated at Trinity College, Toronto. Various members of his family, leaders in their respective professions, have resided in the latter city. As his reputation grew, it was only natural that his influence on the profession in the two older provinces of Canada should have been very great.

After his graduation from McGill in 1872, he spent the next two years in research work abroad, at University College, London, and at Berlin and Vienna, where he formed associations with such men as E. A. Schäfer, Virchow, Nothnagel and others. While abroad, he published in 1873 his researches on the blood platelets in which he established their corpuscular character. Upon his return to Montreal in 1874, he was appointed professor of the institutes of medicine, at McGill University, a position he filled until 1884. During this period, he was brought into intimate association with his old teacher, Robert Palmer Howard, who was professor of medicine and dean of the medical faculty, and with those able clinicians, Ross and MacDonnell. His natural bent for research and investigation, had been further stimulated by his experiences abroad. A full appreciation of the importance of the microscope in medical research led, upon his return, to its more extensive adoption in the laboratories of McGill. While there, Osler laid the foundation of his keenness as a clinician, through his recognizing the great importance of following the fatal cases to the autopsy room, performing many of the necropsies himself. These investigations resulted in the publication of numerous important contributions to medical literature. Among these may be mentioned his paper in which mycotic aneurisms in association with ulcerative endocarditis were described for the first time, and his account of the ball-valve thrombus at the mitral orifice, which also was the first recorded case.

He was very much interested in comparative pathology, and performed many autopsies on lower animals with that keen veterinarian, Clements, who later went to Baltimore, where he died an untimely death from myocardial disease.

Many of Osler's students of this period are scattered throughout Canada and the United States, and they look back with pleasure and profit to the training and stimulus they received under him at McGill. One of the powerful influences he possesses was manifested, even in these early years, through his readiness to report interesting observations before local medical societies and provincial medical associations, and to encourage others to do likewise.

Osler's contributions to medical literature while at McGill, and his papers read before medical societies in the United States, naturally attracted a great deal of attention, and, when in 1884 the University of Pennsylvania was seeking the best trained man to fill the chair of professor of clinical medicine, Osler was its choice. While in Philadelphia he was brought into close association with such men as Weir Mitchell, William Pepper, Tyson, Musser, Keen, Wilson and others. His influence on medicine in the United States was very marked even during this Philadelphia sojourn from 1884 to 1889. He was one of the original members of the Association of American Physicians, which was organized in 1886 with Francis A. Delafield as its first president. He always took an active interest in the annual meetings of the association, contributing numerous original papers and entering into the discussions. He was himself its president in 1895.

While at the University of Pennsylvania, Osler's contributions to medical literature were numerous and important. Much of his material for his monograph on the "Cerebral Palsies of Children," published in 1889, was gathered during this period. His experience at Blockley, that wonderful storehouse of clinical and pathological material, provided him with a mass of data later freely utilized in the preparation of his text-book.

In 1889, as the construction of The Johns Hopkins Hospital was nearing completion, the trustees of the university and hospital, seeking the best man to fill the chair of professor of medicine in the university, and the position as physician-in-chief to the hospital, at once thought of Osler, who was then considered the most brilliant clinician available. The offer was tendered and accepted, and he was on duty when the first patient was admitted to the hospital on May 10, 1889.

It was during his period of residence in Baltimore from 1889 to 1905 that Osler's influence on medicine in the United States and Canada was chiefly exerted. In making appointments to his hospital staff, graduates of medical schools in both the United States and Canada shared the privilege of working under him. Owing to his close affiliations with teachers in the Canadian medical schools, it was only natural that these men should be appealed to from time to time to supply assistants for its interne staff. His first resident physician was Lafleur, of McGill, who during his tenure collaborated with Councilman in the publication of their important monograph on amœbic dysentery. Lafleur, as have other assistants, returned

to Canada and carried with him to McGill and the Montreal General Hospital the stimulus and methods acquired while under Osler. Hewetson, also of McGill, soon followed Lafleur as an assistant. The unfortunate development of tuberculosis prevented him from pursuing what promised to be a brilliant career. Thayer, of Harvard, who now holds the chair in medicine on the whole-time basis, succeeded Lafleur as resident physician and served until 1901.

J. E. Graham, who was for many years professor of medicine at Toronto University, an excellent clinician and a man much beloved by his students, was a close personal friend of Osler. Through him several Toronto University graduates became assistants of the latter. Among these may be mentioned, Barker, Parsons, Thomas McCrae, the late John McCrae—the immortal composer of “In Flanders’ Fields,” Gwyn, and the writer. It may be of interest to note that all these, with one exception, were previously resident physicians during the summer months at the Robert Garrett Hospital for Children at Mt. Airy, Md., which was under the direction of Dr. Walter B. Platt. Barker, later succeeded Osler, as professor of medicine. The writer, and Thomas McCrae, in turn succeeded Thayer as resident physicians. W. G. MacCallum, now the professor of pathology at Johns Hopkins, although a medical graduate of this university, but a graduate in the academic department of the University of Toronto, was, after graduation, an assistant on Osler’s staff. Mention is made of these various Canadians to point out how Osler acted as a magnet to draw them from across the border to Baltimore, and to emphasize the fact that they have, through their “chief,” indirectly constituted an important link helping to keep up intimate associations between the profession on both sides of the line.

Following Thomas McCrae, the resident physicians, with the exception of B. A. Cohoe, a medical graduate of Toronto University, who served from June to September, 1908, have all been graduates of The Johns Hopkins Medical School. They have been in succession, Rufus I. Cole, Charles P. Emerson, Thomas R. Boggs, Frank J. Sladen, Paul W. Clough and the present occupant, Arthur L. Bloomfield. Cole was the only one of these who served as resident physician during Osler’s occupancy of the chair of medicine, although Emerson and Boggs were assistant resident physicians under him before he left for Oxford, in 1905. Osler’s ideals and influence have

been disseminated by this group of resident physicians in the various fields in which their activities have been cast.

The first edition of Osler’s “Principles and Practice of Medicine” appeared in 1892. This, and the subsequent seven editions, have been the standard text-book in medicine used by students and practitioners in both the United States and Canada. The influence of this work, with the fascinating and practical way in which the various diseases were treated, has been very great on the professions of both countries. The same can be said for the two editions of “Modern Medicine,” of which he was chief editor, Thomas McCrae being associated with him.

Throughout Osler’s professorship at Johns Hopkins, courses to post-graduates were given yearly. The medical school was not opened until 1893, and under-graduate instruction in medicine consequently did not begin until 1895, so that, up to that year, post-graduate instruction was the only teaching conducted in the medical wards. Osler’s ward clinics and clinical lectures were attended by physicians from all parts of the United States and Canada. Members of the profession rubbed shoulders, gained invaluable clinical experience, and formed professional ties and friendships which have continued ever since.

Although domiciled in the United States, the Canadian profession always felt that it had a personal claim on Osler. His trips to Canada to see his family in Toronto, to consult with physicians, to read papers before societies in various parts of the Dominion, and often to spend his vacation on the lower St. Lawrence, enabled him to keep in close touch with the profession of his native land and to exert a strong influence on its members north of the border.

Almost as important a sphere of influence as The Johns Hopkins Hospital was Osler’s home at 1 West Franklin Street, where physicians from both sides of the line were always welcome, and where they were ever made to feel at home by the “chief” and his gracious wife, now Lady Osler.

In 1905 Osler was called to Oxford to occupy the chair of Regius Professor of Medicine in that university. His interest in the medical profession of both countries has not a whit abated. The home of Sir William and Lady Osler, at 13 Norham Gardens, has been almost a daily rendezvous for the khaki-clad medical officers of the American and Canadian Expeditionary Forces during the last two years of the world’s war.

OSLER AS A CITIZEN AND HIS RELATION TO THE TUBERCULOSIS CRUSADE IN MARYLAND

BY HENRY BARTON JACOBS

Though Osler like Nathan Smith, Austin Flint and Marion Sims and the philosophers of old is essentially a peripatetic, a medical nomad, yet wherever his feet may take him, there he establishes and identifies himself, interests himself in local conditions and undertakes the responsibilities of citizenship.

In the course of his wanderings Baltimore has had the privilege and the profit of halting his onward steps for fully

sixteen years. Here he came in the vigor of his promising 40 years, trained and ready, not to say anxious, to jump into the life of his new surroundings. Many paths there are which lead to useful citizenship—Osler chose one peculiarly his own, and followed it consistently and unflinchingly, guided only by the unswerving conviction that whatever he might do to advance and improve conditions in the profession to which he was

allied, in that way alone could he be of the greatest benefit, not only to those immediately under his tutelage or care, but to the city and to the nation at large. In his final address on leaving Baltimore he says "I have lived my life in my beloved profession. . . . I have never departed from my ambition to be first of all a servant to my brethren."

The advancement and improvement of medicine and service to his fellows, therefore, is the primary path of his endeavor. The wayside results of such a course pursued with intensity, with kindness, with sympathy, with laughter and joke, with good fellowship and hospitality, also with hard study and thought and work, diligently and persistently, year by year, are quite unusual, and lead as is only natural to wide friendships, extraordinary and general influence, both with individuals and with peoples.

Scarcely had he arrived in Baltimore in the spring of 1889 when he was asked by the officers of the State Medical Association, the old Medical and Chirurgical Faculty of Maryland, to deliver the oration at the annual meeting of the society to be held in April of that year. This invitation he accepted, choosing for his topic "The License to Practice." At this period it should be recalled there were in Baltimore no less than four or five medical schools with two-year courses of study for a degree to practice, and this degree the only license required. The argument Dr. Osler made in his address was so cogent, so direct, so illustrative of the evil conditions existing that immediate steps were taken by the leaders of the medical profession of the city and state to have prepared a legislative Bill for the appointment of medical examiners whose duty it should be to examine candidates, and to issue to the successful ones licenses to practice. This was Dr. Osler's first effort in Maryland toward the advancement and improvement of medicine, and coincidentally his first pronounced effort in good citizenship. As a farther resultant the University of Maryland decided to lengthen its course of medical study and to raise its standard. Moreover, the seed was growing so fast that in February, 1890, a meeting of representatives of all the medical schools of Baltimore decided to request delegates, from the medical schools of the country, to meet in Nashville with the idea of raising the standard of medical schools all over the United States. At this conference an agreement was reached for a three-year course and other reforms.

The Legislature of 1890 passed the Bill for the appointment of a board of medical examiners, a bill which looked to the betterment of medical practice in Maryland and to the general elimination of the numerous quacks and charlatans who had been permitted to carry on their trade in the state. Unfortunately Governor Jackson did not give his approval, and so two years had to go by before its final adoption by a new Legislature, and the signature of Governor Brown. This was but the beginning of Dr. Osler's efforts for better state and municipal laws.

The almost unrestricted prevalence of typhoid fever in the United States, particularly in Baltimore, was a source of deep aggravation to him, and called for the use of all his

powers of voice and pen to bring light into the darkness, that rational legislative measures might be inaugurated to restrict its incidence.

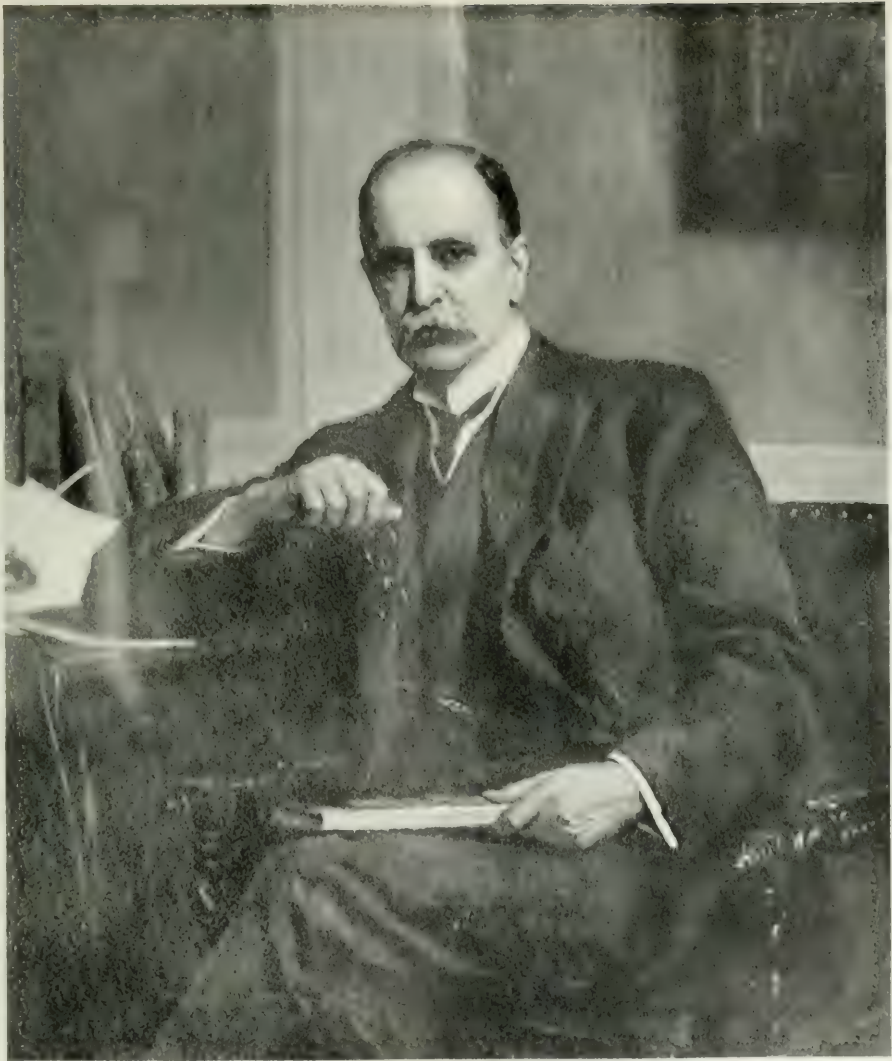
Baltimore at this time was without a general system for the disposal of its sewage. Backyard privy vaults were nearly universal. Dr. Osler was strongly of the belief that typhoid fever would be greatly reduced with the introduction of a proper and adequate sewerage system and a pure water supply. Note how vividly and forcefully he spoke at the meeting of the Maryland Public Health Association held on November 13, 1897, upon the subject of mortality from typhoid fever as related to these important city improvements:

The penalties of cruel neglect have been paid for 1896; the dose of victims for 1897 is nearly complete, the sacrifices will number again above 200. We cannot save the predestined ones of 1898, but what of the succeeding years? From which families shall the victims be selected? Who can say? This we can predict—they will be of the fairest of our sons and of our daughters; they will not be of the very young, or of the very old, but the youth in its bloom, the man in the early years of his vigor, the girl just wakening into full life, the young woman just joying in the happiness of her home. These will be offered to our Minotaur, these will be made to pass through the fire of the accursed Moloch. This, to our shame, we do with full knowledge, with an easy complacency that only long years of sinning can give.

Such writing as this is not only convincing, but is intensely moving, and must have played no small part in securing the desired end which happily came before he was to leave our city, a boon and a convenience to every member of the community, not to speak of the æsthetics of the new order when street and sidewalk gutters were no longer redolent with the morning's dishwashings.

Whatever gives promise of adding to the stock of medical knowledge immediately arouses Dr. Osler's enthusiasm. Early he became interested in the amœbic theory of malaria. Well do I remember his coming to the Massachusetts General Hospital in Boston to demonstrate amœbæ in blood corpuscles to Dr. Fred. Shattuck, then the young medical attendant to that hospital. This must have been in 1887 or 1888. No effort of his for good citizenship, or for the advancement of medicine was more remunerative than the stimulus he gave in this country to the solving of the problem of the causation, cure and prevention of malaria, a disease which had so sorely afflicted the people of states south of Mason and Dixon's line. Baltimore became the prime center for its study outside France and Italy, and Thayer's book written in The Johns Hopkins Hospital from Osler's clinic marks a salutary epoch in the history of this mosquito-borne infection.

Never was it out of Dr. Osler's mind that a better educated and more widely read medical profession made for better living conditions of the people, greater civic comfort and diminished suffering and death, so in all ways possible he encouraged students and practitioners alike to greater learning. To this end he insisted upon greater comradeship and larger attendance upon medical societies where experiences could be interchanged and interesting cases seen and discussed; he also insisted upon enlarged library facilities, and adequate



ON A PORTRAIT OF SIR WILLIAM OSLER, BART

Portrait by Sir John Everett Millais, 1885

William the Fourth, "God bless the Father!"
I say, "I say, I say, I say, I say, I say,
The Fourth, the Fourth, the Fourth, the Fourth,
I say, I say, I say, I say, I say, I say,
Miles and Miles, Miles and Miles, Miles and Miles,
Not only in the Fourth, but in the Fourth,
With the Fourth, the Fourth, the Fourth, the Fourth,
Hence, the Fourth, the Fourth, the Fourth, the Fourth.

William the Fourth, "God bless the Father!"
I say, "I say, I say, I say, I say, I say,
The Fourth, the Fourth, the Fourth, the Fourth,
I say, I say, I say, I say, I say, I say,
Miles and Miles, Miles and Miles, Miles and Miles,
Not only in the Fourth, but in the Fourth,
With the Fourth, the Fourth, the Fourth, the Fourth,
Hence, the Fourth, the Fourth, the Fourth, the Fourth.

By Sir John Everett Millais, 1885

supplies of current medical magazines and standard books. Under his inspiration and leadership the old state society of Maryland took on a new life, and its library so long mouldering on its shelves sprang into usefulness. To him more than to any single man does the medical profession of Maryland owe its present faculty building with its large and growing library—a library in which he took no less interest than in his own. To this extent, then, we must think of him as contributing enormously to the welfare of the community through an enlightened profession influencing public opinion in matters pertaining to health, sanitation, and general hygiene.

Not less than his trenchant writing and speaking was Dr. Osler's own personality of influence upon men and the community; so strikingly straightforward, so genial, even convivial, so playful in youthful spirit, so enthusiastic in helpfulness and sympathy, so painstaking and so wise, he soon had both patients and acquaintances alike in an attitude of devotion, almost, I might say, of adoration. And although he took no official part in the civic affairs of the city, he gained through his association in the medical profession, by reason of his acknowledged eminence in that profession, and through his friends and acquaintances, a leadership in the affairs of the city and state which was most powerful and beneficent even though it was exercised in an indirect way.

From the moment when Koch discovered the germ of tuberculosis in 1882, Dr. Osler has never lost interest in this disease. He dwelt upon it in his teaching and he insisted that his students should be familiar with it. When in 1892 the use of tuberculin was thought to be specific, he was among the first in this country in giving it a thorough trial in the wards of the hospital. For greater encouragement to the study of the disease, which so long has been such a fatal enemy of mankind, he suggested and carried out the establishment of a society whose single purpose should be the consideration of the history and the various phases, clinical and pathological, of tuberculosis, and this society he named, after the great French student of tuberculosis and discoverer of the stethoscope—*The Laennec*.

On November 14, 1899, Dr. Osler read an important paper on the "Home Treatment of Pulmonary Tuberculosis," at the semi-annual meeting of the faculty at Westminster, and on the same day and in the same place Dr. Charles S. Millet of E. Bridgewater, Mass., described his outdoor sleeping porches for tuberculous patients. This was the first public discussion of the value of unlimited night air in the cure of consumption and marks a new epoch in the method of treatment. Incidentally I may remark that at this same meeting mention was first made by Dr. Joseph E. Gichner of the need and desirability of a State Sanatorium in Maryland.

On April 19, 1901, at the invitation of Dr. Osler, Dr. Lawrence F. Flick of Philadelphia came to Baltimore and before the Clinical Society delivered an address on the "Registration of Tuberculosis," saying that Philadelphia and New York had already inaugurated such a provision. Dr. Osler urged that Maryland should do likewise, as in this way the location of cases could be known to the health authorities

and such steps be taken as would be of advantage to the patient and to the community.

By the end of the year 1901 there had arisen great interest in the tuberculosis movement, and it was proposed that the Legislature of January, 1902, should pass new and vital laws which should be of benefit to the whole people. To this end a big meeting in McCoy Hall was proposed under the auspices of the Maryland Public Health Association, the Medical and Surgical Faculty of Maryland and the Laennec Society. Dr. Osler's "fiery" speech thrilled the audience:

Mr. Chairman and my long suffering, patient, inert fellow-citizens: . . . now what is our condition in this city, and what are we doing for the 10,000 consumptives who are living today in our midst? We are doing, Mr. Mayor and fellow-citizens, not one solitary thing that a modern civilized community should do. Through the kindness of a couple of ladies—God bless them!—I have been enabled in the past three or four years to have two of the medical students of The Johns Hopkins University visit every case of pulmonary consumption that has applied for admission to the dispensary of our hospital, and I tell you now that the story those students brought back is a disgrace to us as a city of 500,000 inhabitants. It is a story of dire desolation, want and helplessness, and of hopeless imbecility in everything that should be in our civic relation to the care of this disease.

He then argues for registration, disinfection after death or removal, a State Sanatorium for curable cases and a hospital for advanced cases, a sewerage system and a hospital for contagious diseases. This address and others made the same evening had an effect, to wit: The Legislature of 1902 created a Tuberculosis Commission, the Governor naming Dr. Thayer as its chairman.

All that is progressive or worth while in the Tuberculosis Crusade in Maryland followed thereafter; the commission with its advisors taking the initiative in beneficial measures. At Dr. John S. Fulton's suggestion the commission decided upon a tuberculosis exposition in January, 1904, which should show graphically and practically the general incidence of tuberculosis, its methods of prevention and cure, its etiology and pathology, its relations to social and economic problems, and a history of its study from the time of Hippocrates. Such an exposition for any single disease had never before been attempted. Lectures and demonstrations were given and the attendance not only from Baltimore but from the counties and from outside the state was remarkable. The public was intensely interested and the exposition "demonstrated that it is both expedient and practicable to admit the general public to free participation in the scientific knowledge of tuberculosis." (Editorial, Md. Med. Jour.)

Dr. Osler was the moving spirit in this most successful undertaking and it was he who invited the distinguished speakers who were heard. As a result of this exposition, the Legislature of 1904 passed laws requiring:

- (1) Registration of tuberculosis in Maryland, and
- (2) Providing means and measures to be administered by the State Board of Health for the domestic prophylaxis of consumptives.

Growing out of this exposition, too, was the formation, fol-

lowing the suggestion of Dr. S. A. Knopf, of the National Association for the Study and Prevention of Tuberculosis. In this enterprise Dr. Osler had a leading part. In its organization he was made vice-president, and since his residence in England has been continued one of the two honorary vice-presidents, Mr. Roosevelt being the second.

In December, 1904, the Maryland Association for the Prevention and Cure of Tuberculosis was formed and again to this local movement Dr. Osler lent his interest and enthusiasm. His last effort for the tuberculosis cause in Baltimore was to induce Mr. Phipps to give the sum of \$10,000 for a Tuberculosis Dispensary at The Johns Hopkins Hospital. This was opened with addresses on February 21, 1905, Mr. Phipps being present.

In reviewing thus briefly the activities of Sir William Osler during his sixteen years in Baltimore, I realize how inadequately I have been able to convey any idea of his great work and influence, or the universal esteem, love and honor in which he was held not only by the people of Maryland, but by the country at large. I cannot believe that any man ever left our shores for a new work elsewhere more deeply and sincerely missed by a larger army of friends. His address of farewell delivered before the Medical and Chirurgical Faculty of Maryland April 27, 1905 on "Unity, Peace and Concord" typifies his attitude to all his fellows both professional and lay. In closing he sums up this relationship in the one word which he leaves as his benediction—CHARITY—and the greatest of all is Charity.

OSLER'S INFLUENCE ON OTHER MEDICAL SCHOOLS IN BALTIMORE HIS RELATION TO THE MEDICAL PROFESSION

By EDWARD N. BRUSH

To estimate correctly Osler's influence upon other medical schools and upon professional thought and conduct would require an inquiry into the methods of medical teaching in vogue more than a quarter of a century ago, and into the social and professional relations of the physicians of the city and state toward each other.

At about the time of Osler's arrival in Baltimore to assume the duties of physician-in-chief to The Johns Hopkins Hospital there was a movement on foot to improve and enlarge the medical curriculum. The University of Maryland in 1889 announced that after 1891 a compulsory three-year course would be required in the medical department with a preliminary examination in English.

In March, 1890, a call was issued by the medical staff of The Johns Hopkins Hospital, and the medical faculties of the University of Maryland, The College of Physicians and Surgeons, The Baltimore Medical College, The Baltimore University and the Woman's Medical College for the organization of a medical college association with a view to the co-operation of all medical teaching bodies in bringing about a three-year graded course, written and oral examinations, a preliminary examination in English and laboratory instruction in chemistry, histology and pathology.

At the meeting of the Medical and Chirurgical Faculty in 1889 the annual address was given by Dr. Osler, who took for his theme "The License to Practice," and undoubtedly this address gave an impetus to a movement, already receiving support, for higher medical education and a better qualified student body.

My own connection with medical teaching in Baltimore did not begin until eight years subsequent to this date, but I realized before that period, and have had occasion to know since, the great interest which Osler took in promoting reforms in medical teaching not only here, but in the country at large, the great and lasting influence of his advice, and above all, his example as a teacher.

Trained as he had been as a laboratory man, realizing to the fullest extent the results which flowed from his laboratory studies and their bearing upon the practical work of the hospital ward and the consulting room, as well as in the lecture hall, he urged the establishment of laboratories.

Thoroughly equipped laboratories, in charge of men thoroughly equipped as teachers and investigators, is the most pressing want to-day in the medical schools of this country.

The hospital was, from his point of view, a college—a place of teaching, the most essential part of the machinery of a medical school.

The systematic use of the resources of the hospital which he inaugurated and which he urged upon other communities and described in detail in his address before the New York Academy of Medicine in 1903 found in the minds of the more progressive teachers of the Baltimore schools a ready acceptance.

For those working in my own special field, it is gratifying to believe that it was a few words spoken in his farewell address at the university, February 22, 1905, which gave an impetus that resulted in the establishment of a psychiatric clinic at the hospital.

From his address at the dedication of the Wistar Institute of Anatomy and Biology of the University of Pennsylvania, 1894, I take the following:

What, after all, is education but a subtle, slowly effected change, due to the action upon us of the externals; of the written record of great minds of all ages, of the beautiful and harmonious surroundings of nature and art, and of the lives good or ill of our fellows—these alone educate us, these alone mould the developing minds.

The whole career of Osler in Baltimore, his life here as a teacher, hospital physician, consultant and citizen was devoted to the better teaching of medicine, to better ideals in education; and from his life, from his example, proceeded influences which not only moulded developing minds, but stimulated all

who had a real ambition, to teach and, in teaching, to learn also, and develop.

To emphasize sufficiently his influence upon medical education is most difficult. One of his constant pleas for other schools was for larger clinical advantages, and better use of those already provided. In 1897 in his address on Internal Medicine as a Vocation, before the New York Academy of Medicine, he says:

To-day the serious problem confronts the professors in many of our schools—how to teach practical medicine to large classes; how to give them protracted and systematic ward instruction? I know of no teacher in the country who controls enough clinical material for the instruction of classes, say of 200 men, during the third and fourth year.

Never a controversialist, none the less did he bear a large share in the controversies of 30 or more years ago, which preceded and eventually brought about the changes in the methods of medical education which have taken place since that time. His influence was exerted not in argument or controversy, but in the force of example, by the way in which he lived his ideals and induced others to share them with him.

He studied "to be quiet" and do his "own business," "to walk honestly toward them that are without" and one of his chief pleasures was "to work among [us] as a friend sharing actively in [our] manifold labors."

Some years ago I had occasion to apply to him a quotation from the presidential address of the late Dr. Charles M. Ellis before the Medical and Chirurgical Faculty in 1898. These words seem to me particularly appropriate to Dr. Osler:

Many [doctors] by reason of natural endowments and acquired fitness elevate their lives to a professional plane on which it is possible for an intellectual life to develop; and on which it does develop, not only to individual sufficiency, but to public usefulness and a public influence, that on the one hand meets and supplies public emergencies and, on the other, largely directs and controls public thought and movement.

These words from what I know of the intimate and friendly relations between the two men may well have been brought to the mind of Dr. Ellis by his knowledge not only of the intellectual life of Dr. Osler, but by his appreciation of the controlling influence of his mind upon public thought and movement, particularly in professional circles.

Very early in his residence in Baltimore, notwithstanding that he "studied to be quiet," he became a by no means unimportant factor in the social life of Baltimore physicians.

He so regulated his work that he always had a certain

amount of time to give to his friends in social converse, or in conference over the more serious things of their everyday lives and work.

He appreciated the difficulties and perplexities which surrounded the lives of many of his professional brethren and many a burden has been made lighter, many dark hours brightened, by his wise and thoughtful advice and his cheering optimism.

More than one doctor laboring amid discouragement and the indifference of open opposition of his fellow-citizens, whose lives he was manfully trying to make more tolerable, whose surroundings he was endeavoring to make more healthful, has found to his surprise that Osler had learned of what he supposed was unknown beyond the bounds of his own community, and has received from him words of cheer and commendation, which were a powerful incentive to renewed effort, just when all the uses of the world appeared to him "weary, stale, flat and unprofitable."

His farewell address "Unity, Peace and Concord" is an eloquent recital of his consuming eagerness to be "a servant" to his brethren to do all in his "power to help them."

He strove always to live in unity, peace and concord with his fellows. He strove with none—not that none were worth the strife, but because of a deep conviction of the hatefulness of strife. Those worth the strife he won by other and gentler means, and bound them to him by the everlasting chains of friendship.

In 1881 there was formed in Baltimore the Baltimore Monthly Medical Reunion. It met at the home of members in turn and around the dinner table and at the fireside many friendships were made and consolidated. Very soon after coming to Baltimore, Dr. Osler became a member of the Reunion and always when he was present at the monthly gatherings, as with The McGregor, where Osler sat was "the head of the table," the center of conversation, the focus of wit and wisdom.

As in the past, so in the future in all that makes for truth and righteousness, in all that holds forth high ideals, in all that encourages culture and all the virtues of the Christian gentleman and the ideal physician the name of Osler will be one to conjure with. From time to time, as on the present occasion, his friends for many years, let us hope, will send him greetings across the sea. He has given us the master word and with that in our hearts all things are possible. Have we not seen it exemplified in his life and character?

INFLUENCE IN BUILDING UP THE MEDICAL AND CHIRURGICAL FACULTY

By HIRAM WOODS

"Influence in Building Up the Medical and Chirurgical Faculty" is a theme one might approach from numerous paths. So great was Dr. Osler's influence, in so many directions did it work, so broad was his conception of the possibilities for good in the organization, so keen his appreciation

of the obstacles to progress, some traditional, some personal, that the many-sided subject is bound to appeal to his friends in different ways. Adequate organization of the library; revelation to the younger man of what the library even in those days afforded; provision for the purchase of new books—these

are themes which have been selected for special review and will be presented by others. I shall try to give some idea of his work from another standpoint—that of personal influence. Yet, with the selection of this special topic, I am aware that I shall speak from my own personal impressions and memory and may fail utterly to express the feelings of another just as indebted to Dr. Osler as am I.

I have asked myself, What were Dr. Osler's basic thoughts and principle in his work for, and devotion to, the State Medical Society? He held the most influential position medicine in Baltimore could give; he had at command greater powers than any one medical man had ever possessed in the city; his teaching and organization duties in the new medical school were exacting enough to take all his time, and yet he went to work on the state society in a way which soon gathered recruits happy to work under—not his direction—but his mind and heart. What led him to do it? I think he felt that the biggest medical foundation Baltimore had ever had ought to benefit the existing profession. He thought there should be a high valuation of the profession itself; realization of the obligation of self-improvement; a breaking-down of the "middle wall of partition" between those, who, by a connection with the new school, seemed to possess an advantage, more or less adventitious, and those who found, or thought they did, a definite obstacle to practice in the new Foundation. He felt the meaning of "Unity." He told us of this—at least in words—only on the eve of his departure. And yet he had told us about it previously in a better way. Go over the papers he brought to the faculty meetings and the smaller gatherings of the local society and you will, if I mistake not, see that he presented the problems of disease, cause, prevention and cure, as the same for the hard-worked country doctor, with little time to read, and the man with hospital and laboratory advantages, plus trained nurses and competent assistants. But here the roads parted, in a sense. The practitioner brought his experiences and difficulties. Modern methods of investigation were not at his command. Dr. Osler felt that the man with greater advantages should, in the first place, qualify himself to understand the point of view of his less fortunately placed colleague, and then, from his greater advantages, make up the deficiency.

Sometimes a chance thing makes a life-long impression, and such an occurrence has come back to me time and again. At a society meeting typhoid fever was the topic. I believe I am quoting accurately: "Typhoid fever, the monster that destroys the best of our sons and claims the fairest of our daughters; are we to let it continue or stop it?" And then followed a clear, scientific and yet almost a domestic demonstration of preventive measures which could be taken home and taught to those who did not know, but who, if they knew, might save their own and others' lives. This, I believe, was Dr. Osler's motive force: aim to realize the other man's point of views and his needs, and to reach these needs if he could. But if such was the self-imposed task, success could come from no wiser-than-thou attitude. There had to be a comradeship; not the assumed, patronizing variety, but the sort that cements

the minds and hearts of men earnest after the same thing—knowledge. How many of us have met him browsing around in the library, and soon found ourselves just talking? Yet from that talk we afterwards found we had gleaned a great deal. It was from one such talk that I took away definite impressions about the evils of narrow specialism. Again, after we got to know him better, we would sometimes find him in deep conversation with a beginner in medicine, or a man we hardly knew, and we shied off. It was perfectly clear what he was doing. But the comradeship was the real thing; there was nothing professorial about it. This comradeship extended beyond the confines of men who were active students for their own good or those who needed prodding. It went after and reached those who had something to give, and who did not know how to give it; maybe they did not know they had it. There are matters of importance to the faculty and profession, bearing others' names, which would never have come into being without William Osler's realization of their importance and pointing out the way to achievement. I cannot speak more definitely; but men familiar with the faculty's history will know. This comradeship went farther. It reached those who for one reason or another had met with little or no success. It made them feel that in spite of what might be termed failure, honesty of purpose gave standing to a man in medicine and brought him into unity with his brothers upon whom fortune had smiled more kindly.

Work for the library, teaching its value by precept and example, demonstrating the unity of the medical profession and the spirit of comradeship soon won the esteem, confidence and affection of men throughout our state. This feeling was, possibly, best expressed in a telegram sent to Dr. Osler's mother in April, 1905, when he was about to leave Baltimore. The telegram was sent by vote of the faculty at its annual meeting and signed by the president, Samuel T. Earle. It reads:

The greetings of the Medical and Chirurgical Faculty of Maryland to Mrs. Osler, asking her to share their sentiments in taking leave of William Osler, congratulating Mrs. Osler first on the distinguished career of her son, but most on the innate qualities which have endeared him to his associates in Maryland.

A few days later the following reply was received:

Mrs. Osler, who is unable from her great age to write, asked me to express her heartfelt thanks to you for the very kind telegram of greeting sent through you from the Medical and Chirurgical Faculty of Maryland, and to say that the receipt of the message gave her the greatest pleasure, more especially in the expression of affection and appreciation called forth by the personal qualities of her son, since these are, in her eyes, more precious than all his honors.

She knows that it must be hard for him to sever his connection with such kind *confrères*, and she is sure that the friendships he has made during his residence in the States will be among his most cherished memories. I am, sir, yours sincerely,

JEANNETTE OSLER.

One who had thrown his heart and soul into an enterprise would be keenly disappointed if his work fell through in later years. There seems no danger of this while there survive the men who came under Dr. Osler's leadership. The funds

obtained through his influence, and others, which have come since, because of the spirit he put into the organization, are keeping the faculty up to date. But these material things, important as they are, would fail in their purpose, unless something else lived and permeated the faculty's life. I mean the mental attitude which I have tried to present. It is interesting to go over a book in a public library even if one owns a copy himself. The latter he feels free to mark, but it demands a certain amount of bad taste to mark passages in a book which does not belong to you. However, this bad taste does exist here and there and sometimes it may not be without its advantages. It shows the other fellow's thought. Recently I picked up "Aequanimitas" at the library and opened by chance at the delightful essay "Teacher and Student." That a library-worn book like this should open right there is not without significance. It means that there are youngsters coming on now who are getting from the printed page some of the things others got from personal intercourse. This passage is marked with a heavy lead pencil:

The measure of value of a nation to the world is neither the bushel nor the barrel, but *mind*:—wheat and pork, though useful and necessary, are but dross in comparison with those intellectual products which alone are imperishable.

In "Unity, Peace and Concord," written in 1905, 13 years after the essay to which allusion has been made, Dr. Osler speaks of "the petition in the Litany in which we pray that to the nations may be given unity, peace and concord." Then follows this, which I do not attempt to summarize:

Century after century from the altars of Christendom this most beautiful of all prayers has arisen from lips of men and

women, from the loyal souls who have refused to recognize its hopelessness, with the war-drums ever sounding in their ears. The desire for unity, the wish for peace, the longing for concord, deeply implanted in the human heart, have stirred the most powerful emotions of the race, and have been responsible for some of its noblest actions. It is but a sentiment, you may say, but is not the world ruled by feeling and by passion? . . . As with the nations at large, so with the nation in particular; as with people, so with individuals, and as with our profession, so with its members, this fine old prayer for unity, peace and concord, if in our hearts as well as on our lips, may help us to realize its aspirations.

Now, 14 years later, with the world still "refusing" to recognize its "hopelessness" and struggling toward the realization of permanent unity, peace and concord, these words seem almost prophetic. From the "nations at large" through successive steps, this great principle of unity, peace and concord reaches the medical profession and "individual" doctor. His comprehension and use of it will depend on his relative valuation of the "barrel and bushel" and "mind." Dr. Osler's method of upbuilding the faculty differed from others' in that he aimed to increase the individual's receptivity for what the faculty had to offer. So long as the faculty sees its responsibility to offer only the best; so long as its members appreciate the nature of what is offered and remember that profit is a question of their own hearts and minds, there will be no danger of deterioration; but both are necessary. While we are congratulating Dr. Osler and gratefully acknowledging our debt to him, let us not forget what his example taught; for it is only thus that we can keep what he had so large a share in giving us.

OSLER AND THE BOOK AND JOURNAL CLUB

By J. A. CHATAUD

Of all the varied activities and interests that occupied Sir William Osler, while in Baltimore, possibly none appealed to him personally, and to the little group of supporters that he gathered about him in the early days of 1896, more than the idea of getting together a few of the men of the profession at periodic times for the discussion of old books on medical subjects and the presentation of papers on the historical side of medicine. At the same time the members, by their interest in the work and by the voluntary subscriptions offered, helped much in the improvement of the library of the Medical and Chirurgical Faculty by the purchase of new books and journals.

In these early 90's the faculty was in a quiescent mood with few regular meetings at which, for the most part, only routine business was transacted. For lack of funds the library was much neglected and the book and journal files were far from complete. This Dr. Osler saw and at once put his great store of knowledge and earnestness, at the disposal of the members of the faculty, with the result that the Book and Journal Club was soon in a flourishing condition.

Those of us who went to the early meetings can still remember the enthusiasm of Dr. Osler in his presentation of rare old

historical medical subjects or in the enlightening discussion that he gave following someone else's paper. After some time he would then show some of the fine old books illustrating the talk, these books not infrequently coming from his own medical library.

But for one man's enthusiasm and zeal we might have missed so many interesting talks on the "Hippocratic Writings," the "Plague of 1630 in Milan," "Harvey as an Embryologist," "Some Diseases Bearing the Names of Saints," "The Resurrectionists of London and Edinburgh," "The Books of Vesalius," "Assyrian Medicine," and last but not least, our old friend Sir Thomas Browne. These and so many other historical subjects he was instrumental in bringing before us, leading us on to browse among the old masters and find there the very things we may be looking for to-day.

During his presidency, the Book and Journal Club collected over five thousand dollars by voluntary subscription and in addition to paying for the binding of many journals, we were able to purchase annually about 270 books and subscribe to 56 journals. To those of us who know how crippled the

finances of the faculty were at that time, and how little was available for the library fund, this money from the Book and Journal Club was a treasure indeed.

To the older members of the faculty his work and zeal for their interests was of wonderful help and assistance, and his close association with them will always be looked back on with the deepest and most lasting pleasure. To the younger, some of whom are now among the older members of the faculty who knew him at that time and worshipped from afar,

his example should be a help to be better students and workers. To the youngest members of the faculty, who, alas, knew him not, it becomes a duty to emulate his efforts in historical study and so join in the company of those who can find that all is not dry and musty in the old discolored books upon our shelves. It is only by thus fostering and helping along a search for old truths that the newer ones assume a more crystalline appearance and we are better able to value them in the light of advancing thought.

OSLER'S INFLUENCE ON THE LIBRARY OF THE MEDICAL AND CHIRURGICAL FACULTY OF THE STATE OF MARYLAND

By MARCIA C. NOYES, Librarian

Associations of Dr. Osler are so interwoven with the library of the Medical and Chirurgical Faculty that what we have become is, in reality, but an expression of what we felt he would have us be.

The name of Osler is writ large in the history of the library from the time of his first connection with it in 1890; and the impression made by his character on the lives of those with whom he came in contact has been a powerful influence for the betterment of medicine in Maryland and in the upbuilding of the state society and its library.

Dr. Osler was elected a member of our Library Committee in 1892 in which year the committee reported difficulties, financial and otherwise, in the management of this "most valued and noble inheritance." Although never serving as chairman, that he lent himself to the surmounting of these difficulties we know, and what was accomplished between 1892 and 1905, his tenure of office on the Library Committee, is given, in part, herewith.* From a collection of a few thousand old books in 1892 it grew to 14,590 volumes in 1905, and has grown steadily ever since.

The library, which dates from 1830, had been partially revived in 1881 and was housed in rooms in the basement of the old Maryland Historical Society in 1885; but it was Dr. Osler's interest which brought about its renaissance and the purchase of and its removal to the home at 847 N. Eutaw Street (Hamilton Terrace) in 1895. After a year without proper supervision it was owing to Dr. Osler, who personally saw to it, that the Library Committee employed a trained worker and the present

librarian took charge. To him we owe the founding of the Charles Frick section of the library, in 1896, which was made possible by the generosity of Messrs. William F. and Frank Frick; and the establishment of the Book and Journal Club at about the same time. These funds gave the Library a definite income for the first time in its history.

Dr. Osler was president of the Faculty in 1896-1897, and in his presidential address, April, 1897, in outlining the purpose of the Book and Journal Club, and of the Frick memorial said: "I envy Charles Frick the good fortune to go down to the future generations in this Faculty with his name linked to an important section of our library. Posthumously and by proxy, as it were, thus to carry on, though dead, the work he was interested in while living, is the nearest approach a man can make to cheating the great enemy, and in Charles Frick's case it is in a measure a compensation for the untimeliness of his taking off." He also spoke of the approaching centennial as follows: "We can try in the centennial year to obtain a proper endowment for the Faculty from our friends among the citizens. We shall need a larger hall, more in keeping with the rank and work of the profession of this city—quarters as complete as our brethren enjoy in Philadelphia and New York. And an endowment yielding a few thousand dollars annually is absolutely essential for the proper development of the library." At the centennial of the Faculty in 1899 he gave the first thousand dollars toward such an endowment fund; and it may safely be said that it was principally due to his influence that the Charles M. Ellis bequest was made in 1910.

It was because of the widespread desire to honor Dr. Osler that the present home of the library, at 1211 Cathedral Street, became a fact in 1909; and because of a further expression of



* When abroad for his annual outing, Dr. Osler always had the needs of our Library in mind, and we owe many of its greatest treasures to his interest. Some of these were a direct gift from him, and others selected for purchase on the Frick Fund.

this desire that the Osler Testimonial Fund for the purchase, in his name, of books on medicine was presented to us in 1917. It is singularly fitting that his name should be linked for all time with that of the Medical and Chirurgical Faculty and its library, for he delighted so keenly in the phrasing of the old title—the chirurgical, so hard for the uninitiated to pronounce—and in the usage of the word faculty instead of society. The development of the library, to its fullest extent, interested him beyond measure, for he was not only a lover, but a user of books, and he insisted that his students should learn the art. The familiar slip bearing his reference was presented almost daily by some one of them, and our reading room on Saturday afternoons became a rendezvous for students and physicians who thought to meet him there to seek his advice. In those days, the pausing of a hansom at the door, if followed immediately by a cheery whistle, presaged his advent to the initiated. Hardly a Saturday passed without Dr. Osler coming to scan the shelves containing the new journals and to browse among the books to be found in the Charles Frick Reading Room.

Akin to his interest in books is his interest in medical libraries in general, and he was intimately familiar with and always a welcome guest at the library of the Surgeon General's Office, the College of Physicians of Philadelphia, the New York Academy of Medicine, the Boston Medical Library and the library at McGill University, as well as the libraries in Baltimore and many of the smaller medical libraries elsewhere.

some of which he fostered. He was not only familiar with the books in these collections, but he knew intimately the catalogers and workers who do not usually come in contact with the readers, as well as the librarians in charge.

This interest found expression in the founding, in conjunction with Dr. George M. Gould, of Philadelphia, of the Medical Library Association in 1898. Owing to his generosity our library was a member from the beginning, and has become an influence in the medical world because of this membership and our connection with the exchange of the association.

No one man has so left his imprint on the libraries of two continents as has Sir William Osler, and a quotation from his address "Books and Men" delivered in 1901 at the opening of the new building of the Boston Medical Library, at 8 The Fenway, sums up what his example has meant to this library and Faculty:

It is hard for me to speak of the value of libraries in terms which would not seem exaggerated. Books have been my delight these thirty years, and from them I have received incalculable benefits. . . . For the teacher and the worker a great library such as this is indispensable. They must know the world's best work and know it at once. . . . For the general practitioner a well-used library is one of the few correctives of the premature senility which is so apt to overtake him. Self-centered, self-taught, he leads a solitary life, and unless his everyday experience is controlled by careful reading or by the attrition of a medical society it soon ceases to be of the slightest value and becomes a mere accretion of isolated facts, without correlation.

SOME EARLY REMINISCENCES OF WILLIAM OSLER

By HENRY M. HURD

In September, 1883, while on a vacation trip with a friend. I stopped at Kingston, Ontario, and found myself in a busy throng of physicians in attendance upon the Canadian Medical Association in annual session there. The physicians were diligent in their attendance upon the meetings of the association, proud of their mutual calling and eager to advance it. The secretary of the organization, and one of the leading spirits, was Dr. Osler, a resident of Montreal, a young man of 34 years, who then, as always, appeared younger. He knew in person every physician present and was easily the guiding force in the association. He participated freely in the discussions which followed the reading of papers and did not hesitate to express his mind freely and frankly on all important questions. In the meetings there were the usual differences of opinion between the rank and file of the profession and the members of the medical examining board and verbal encounters sometimes took place between many men of different minds. Osler spoke boldly and without reserve and had an opinion upon all matters, but never seemed to excite ill feeling or lasting resentment on the part of those who differed with him. He was an excellent secretary and carefully watched the progress of the special work of the meetings. He was spare in figure, with a sharp, piercing eye, and although of fallow complexion, was vigorous and in excellent health. He

was neatly and quietly, but carefully dressed and in manner and bearing displayed the characteristics which I later learned to recognize and appreciate as peculiar to him. One circumstance in the meeting attracted my attention in a special way; a prominent member read a paper entitled "The Conduct of Medical Men Towards Each Other and Towards Each Others' Patients," which displayed great wrong-headedness and perversity of feeling in reference to the relations of physicians to each other in the matter of consultations over very ill patients. He held that a physician was justified, when called in consultation, in getting control of his brother practitioner's patient and concluded by saying: "Take all the cases you can get and keep them if you can without reference to the rights of any other attending physician." He also deemed it justifiable to report one's cases of operations or extraordinary cures in the newspapers and inquired, "Why should not medical men report their cases as well as a lawyer his speeches or a clergyman his sermons?" When he had concluded reading his paper he was called sharply to order by several members and referred to the Code of Ethics which existed in Canada to govern the relations of physicians to each other. Whereupon the offender announced that he had never seen any such code and that it had no meaning to him. Dr. Osler sprang to his feet and drew from his pocket a pamphlet copy of the Code of

Ethics which he waved about his head and in a loud, clear voice announced that he took great pleasure in supplying a copy to his innocent and untutored friend and was glad to learn that he had "sinned unwittingly through ignorance."

In 1889, when I came to Baltimore, I found Dr. Osler in temporary charge of The Johns Hopkins Hospital, which had been open in part for a few weeks. He lived at the hospital and guided its work in company with Dr. Halsted and such members of the early staff as Lafleur, Brockway, Clarke and others. I remember on my first visit while walking along Broadway in company with Osler and President Gilman, the day being very hot, the latter, as usual, had an umbrella which he used to protect himself against the rays of the sun. He invited Osler to walk with him, who declined saying, "The chill of nearly 40 Canadian winters is still in my veins and I do not need any such shelter."

He was a delightful companion with children and took much pleasure in conversing with them and even mystifying them by detailing remarkable personal experiences and sometimes tragedies. Once he invited two young girls to a luncheon at his house on Monument Street, where his niece, now Mrs. Abbott, kept house for him. He came late to luncheon and explained his delay by the fact that he had been caught in a down-pour of rain when crossing Monument Square which had produced a flood sweeping him off his feet; that he had escaped only after vigorous swimming and had barely saved himself by grasping the shaft of the Washington Monument with both arms. A more harrowing tale was that of the loss of a young friend by falling from his row-boat into the St. Lawrence River. He explained that he might have rescued her had he not resolved never to act hastily and without due consideration. He had accordingly tossed up a coin to determine what his action should be. It fell adversely and he rowed ashore alone weeping bitterly! Fancy the difficulty of duly impressing high moral precepts upon the young in the light of such a confusing example. Children delighted in his presence and were charmed by him, but very naturally were always uncertain as to the logical nature of his conclusions and equally puzzled by his apparent indifference to conventional conceptions of duty and obligation. There was also in his attitude towards pupil nurses a similar light-hearted irresponsibility which marked some portion of two addresses to nurses to which reference is made later. It is possible, however, to perceive that under the cloak of these apparent trivialities there lurked a seriousness of purpose and a keen desire to point a painful moral in a kindly way. With children, however, it was simply an expression of his ample imagination and of his desire to please and puzzle them. Even older people were sometimes at a loss to follow his moods and strange fancies. He was invariably cheerful, hopeful, and optimistic even under circumstances of discouragement and doubt. I remember on one occasion one of his colleagues, mystified by his imperturbability in a trying emergency said, "Osler drop your mask, let us know what you actually think of the situation," but no one ever did gain that knowledge.

Osler's habits of work, while he resided at The Johns Hopkins Hospital, were exemplary and somewhat unusual for a man of literary taste. Such men are usually inclined to turn night into day, but he rose promptly at 7 a. m., took his bath and breakfast and was ready for work at 8 o'clock. He seemed to have a faculty for setting his mental machinery in motion immediately and accomplished effective work without delay. When his secretary came he generally began to dictate and by practice acquired great facility in terse and vigorous expression. This quality also was undoubtedly assisted by his familiarity with King James's version of the Bible, the Prayer Book, and Sir Thomas Browne. His method of the preparation of the Principles of Medicine was worthy of being followed by other writers. He gathered the literature of any subject which he had on hand by judicious foraging in his library and elsewhere. The volumes thus collected were piled four square generally, open at the page to be consulted upon the table, as long as room sufficed and later upon the floor until movement about the room was much restricted. I remember that when after seven months of strenuous labor he completed the first draft of his treatise on medicine I chanced to look into his room and found that it contained an immense heap of books piled as high as the table like an ancient sacrificial altar. The first draft was carefully revised with no great amount of change in sentences and forms of expression. Such changes as were made, however, did not destroy the crisp, breezy style or the epigrammatic form of expression which has always been characteristic of his literary work. The book contained many personal references which gave peculiar satisfaction to his friends by reason of the good-natured personal touches he frequently gave to the cherished beliefs and traditions which he did not share. I remember in speaking of the use of turpentine in typhoid fever, he said, "The routine administration of turpentine in typhoid fever is a useless practice for the perpetuation of which, in this generation, H. C. Wood is largely responsible." This somewhat pointed condemnation of a generally recognized method of treatment at that time brought forth a vigorous rejoinder from Dr. Wood in a medical journal, but fortunately there was no loss of friendship on the part of either Osler or Wood.

Osler was also very scrupulous in fulfilling his duties in attendance upon the meetings of medical societies. When once informed by a student that he did not attend the meeting of a medical society because he was not sure that he could get anything out of it he replied, "Do you think I go for what I can get out of it or for what I can put into it?" Those who knew him felt a deep impression that in all activities in medical societies and in behalf of his students he labored solely to inspire them with a love of work for its own sake and for what he felt to be its final effect upon their growth and development.

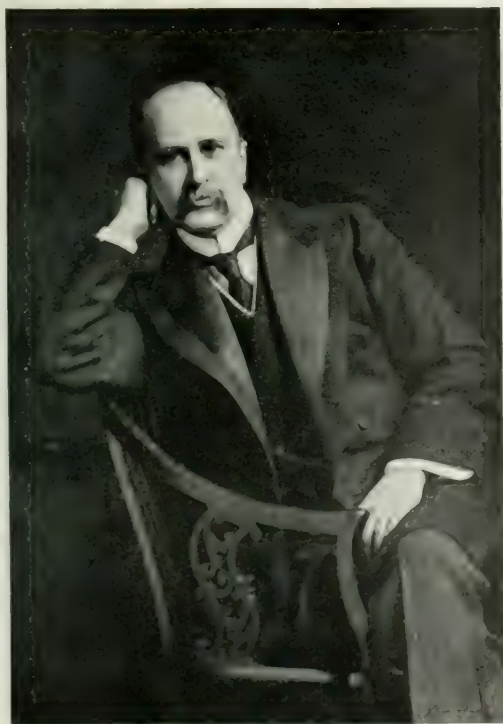
This fact was brought out in his relations to the Training School for Nurses, established at the hospital in October, 1889, which were of an ideal character. He had a warm friendship for Miss Hampton, the organizer of the school and its first principal, and also for Miss Nutting, her successor. He gave



TAKEN IN 1901.



TAKEN IN 1913.



TAKEN IN 1902.



TAKEN IN 1913.

much assistance in the way of advice and in teaching and was warmly interested in its success. He gave two graduating addresses also, one entitled, "Nurse and Patient," and the other, "Doctor and Nurse." He was appreciative of the work of nurses and touched lightly and gracefully upon the mutual relations of the nurse to her co-worker, the doctor, and to the object of her care, the patient. There was, however, a suspicion of an attitude of reserve towards trained nurses as a class as may be inferred by the quotations which preceded these addresses when published. One, for example, had this significant motto, from the Psalms of David, "I said I will take heed to my ways that I offend not in my tongue. I will keep my mouth as it were with a bridle." The other quotation

was from Sir Thomas Browne, "Think not silence the wisdom of fools, but if rightly timed the honor of wise men who have not the infirmity, but the virtue, of taciturnity and speak not out of the abundance, but the well-weighed thoughts of their hearts. Such silence may be eloquence and speak thy worth above the power of words."

Osler in fact seemed always appreciative and helpful while at the same time he had an air of detachment as one who was endeavoring to see whither the movement for the education of nurses would ultimately lead. In the end I am sure that he learned to understand and appreciate the work of the training school and felt the great importance of it to physicians and to the advance of the science of medicine.

OSLER AS I KNEW HIM IN PHILADELPHIA AND IN THE HOPKINS

By HOWARD A. KELLY

I find myself wondering, in these days of pleasant retrospection, now that our much loved friend Sir William Osler is so splendidly rounding out his seventh decade, whether, of all his friends here, I may not claim the credit of having known him first.

I was living in Philadelphia up in the big mill district of Kensington, culling a surgical out of a large general practice, and at the same time keeping in close touch with things at the University of Pennsylvania, for eight years my college, when it became manifest that some fresh and stirring blood had entered the college life.

The university, with so many eminent men camping on her very doorstep in Philadelphia, and with that tendency to nepotism, a form of paternal pride seen in all successful institutions, had, as we younger men thought, driven John Guit  ras of brilliant promise in general medicine, away from her doors to protect Pepper from rivalry, and now, not without great hesitation as we understood, she had actually broken her shackles, thrown traditions to the winds and pulled William Osler down from McGill in Montreal.

Fresh invigorating currents of life and new activities in our stereotyped medical teachings began at once to manifest themselves, and every sturdy expectant youngster in short order lined himself up as a satellite to the new star. Osler breezes were felt everywhere in the old conservative medical center, and yet it was not without some difficulties that he securely established himself. Weir Mitchell, who had reason in his later days to cultivate kindlier feelings towards the university than in his young manhood, was from the first Osler's devoted and intimate friend, and one by one the faculty was won to appreciate him, perhaps including even Pepper too, though I am not so sure. My own life touched Osler's in the Kensington mill district in northeast Philadelphia. Aside from anatomy and chemistry, I got most of my real medical education while a resident in the Episcopal Hospital and next in the homes of the Kensington folk. Wood's physiological therapeutics, and Still  's didactic lectures on medicine seemed

deadly to me, and worst of all was Tyson's pathology elucidated by Formad's quizzes. So it remained to get the education at the bedside, and here Osler came to my aid. It was more than a Sabbath day's journey in those days to go to Kensington from the heart of the city; it was an hour in the street car, and a long drive over bad, very bad, Philadelphia streets, but Osler came and Agnew came with their lamps in their hands to illuminate a few of the problems in the vast domain in which all medical graduates are presumed to be experts.

I think the first patient that Osler saw was suffering from *anorexia nervosa*, a condition which I had never seen before, and of which I was ignorant. He stayed to dine in Norris Square, and was particularly interested in my collection of old medical books.

Then he was whisked away to Baltimore, and then after a year's time, I followed at his behest, glad to have a more concentrated field of work.

Here I can add nothing, for his record is known and read of all men, and what a blessing he, and Welch, and Halsted, and Hurd proved to be in this community. I leave others to appreciate Osler's skill as a medical man, and his love of the classics. I always think of him first of all as one who brought order out of the chaos in the medical profession of this city, a great task effected by his kindly personality, his insight into human nature, and the genuine affection he ever felt for all men who were even half way good.

It was a settled policy of Osler's life never to speak ill of any one but always to find the good, and in that way he converted the hostile camp of Baltimore into a kindly family of cooperating doctors.

Medicine here had fangs in the old days. Osler and Welch more than any others drew them; and so made possible medical progress.

I want to lay claim to the gift of prophetic insight (a r  le I doubt not in which many of my colleagues have anticipated me); I had said from the first that Osler was bound for London, and in the old days I longed to be ready to go with

him when he went. The outcome has exceeded, I think, all our anticipations, and who but he would have maintained unabated the same interest in all his old friends, and who else could have turned the ocean into a highway, and his new position,

detached as it is from any vast clinical facilities, into a veritable medical Mecca for all our American medical world. That many lustra may still be added to the kindly years of Lady and Sir William Osler is the wish of many hearts.

OSLER AS A BIBLIOPHILE

By THOMAS R. BOGGS

Adequate treatment of this important side of Dr. Osler's activities would far transcend the present writer's abilities and the space allotted to this article. But it may be of some value to discuss briefly Dr. Osler's interest in old books as reflected in his informal talks with the students.

In looking back it seems to the writer that the interest in the early editions was a development of the fundamental value he placed in the study of the history and evolution of the science and art of medicine, and that it was in connection with his studies of the fathers of medicine in all times and countries that he began that collection of first and rare editions which has now reached such remarkable proportions.

When the plan of collecting the works of the founders of British Medicine was first originated is unknown to the writer, but it had already reached a large degree of perfection at the time when the class of 1901 began to make the Saturday evening visits to the old house at No. 1 West Franklin Street.

Most of us will ever retain the delightful recollection of those informal gatherings about the big table in the dining-room, when after the discussion of the week's work in the wards was finished, "the chief" would bring out some of the books from the special shelves devoted to the masters of medicine and show us the first editions, tell us the story of their discovery and acquisition, point out the notable passages, and give the salient facts in the author's life history. For many of us this was the beginning of our knowledge of the history of medicine and of our own feeble attempts to follow in his steps as collectors.

How reverently we handled and admired the rare little volumes, of Linaere's grammar, or the spurious first edition of the Religio, or Digby's Animadversions, with their choice bindings by Rivière or Zaehnsdorf. How thrilled by the story of the discovery of such a treasure on a York bookstall, bound in with an Almanack and bought for half a crown. With what delight we turned the pages of the tall copy of the Pseudoxia Epidemica and dipped into the grave Sir Thomas's discussion of the verity of the pictures of God, or the popular idea "that elephants have no knees." A beautiful Aldine from Mead's own library brought out the story of that great collector and his testamentary instruction that his library be sold so that others might have some of the pleasures of acquisition which he had so much enjoyed. We were given a glimpse into the special lore of the bibliophile, and learned something of the work of the pioneer printers and of the great presses of a later

date. We learned a little of the fonts of type and the watermarks of papers, as well as the characteristics of the bindings peculiar to certain periods. The nature of book auctions was disclosed to us and we became familiar with the magic names of Sotheby and Quaritch, until some of us found the perusal of a good catalogue as exciting as a detective story. Still more important, we heard about the more famous collections of medical works, and began to project personal visits to the Bodleian, the Royal College of Physicians and the Bibliothèque Nationale.

But best of all and doubtless the ultimate object of all was the gradual acquisition of an epitome of the history of medicine which has kept us interested ever since those days.

Moreover, it was not merely the cultural value of a knowledge of the beginnings of the profession, but the constant lesson of the individual worker's triumph over handicaps of isolation, poverty, ridicule or personal peril, to add some contribution to the sum of knowledge, and the reiteration of the theme that the painstaking and observant physician, even though removed from the centers of learning and wide opportunity, has in the past contributed fundamentally to the advancement of knowledge, and may hope to do so in the future.

Again, Dr. Osler stimulated in us an interest in the medical writers of the early days of our own country and showed how much might be found by the investigation of the early journals and books, and this has led to the substantial contributions by his associates and pupils to the history of medicine in the colonies, the United States and Canada.

In conclusion, another side of Dr. Osler's bibliophilic activity must be noted, that is, his generous interest in the medical libraries of the country. He was not satisfied to acquire rare and interesting volumes for himself, but was constantly giving such books to the various professional libraries with which he had been associated; thus, McGill, Boston, The College of Physicians in Philadelphia and our own Maryland Faculty and Johns Hopkins have repeatedly received valuable acquisitions from him or from others whom he had induced to give rare volumes or even whole collections.

We are happy to know how vastly "the chief's" collection has grown since he removed to the University of Oxford, so that it is now one of the very best in existence. The catalogue, bibliographic, biographic and literary, of this great collection of the epoch-making works of science occupies most of his leisure, and will form another great contribution to the literature of medicine, second only to the immortal Practice.

OSLER'S LITERARY STYLE

By EDWARD N. BRUSH

There are in connection with the task which has been assigned to me many very pleasant aspects. To make a critical analysis, to present a clear picture of Dr. Osler's literary style demands, however, more time and space than are at my disposal and above all more ability as a literary critic than I am endowed with.

In reading Dr. Osler's contributions to the literature of medicine, as well as his occasional addresses and essays, I am tempted to linger here and there, to point out the clarity of expression, the simplicity and beauty of diction and quote passage after passage in illustration of my thesis. Such a course would simplify the task before me because these quotations would show the author's style better than any powers of description or any ability of analysis I possess.

In his purely scientific work, as for example, in "*The Principles and Practice of Medicine*," the author's method and his grasp of his subject are admirable. He follows the advice of the friend of Cervantes when the author of Don Quixote was in a quandary over the preparation of his preface, "Nothing but pure nature is your business; her you must consult, and the closer you can imitate, your picture is the better."

In my student days some one placed in my hands a copy of Watson's Practice.* While it was not recommended as a text-book to follow as an exponent of the then recognized principles of medical thought and practice, I found it one of the easiest works to read and one from which I obtained much of lasting value. Commenting upon this fact to my preceptor I was told that I had fallen upon a book which possessed, something not common in medical treatises, a good style.

The same is true of Osler's writings upon the strictly scientific aspect of medicine. Unity, order, clarity of description and ease of diction abound throughout his text-book and his various monographs. A master of his subject, having made the nature of disease his business, he imparts his information in such a manner that the reader at no time finds it difficult, because of ambiguous phraseology or doubtful expression, to grasp his meaning. His thoughts are "linked with the wants of his readers," and by the invisible chains which bind mind to mind, he and his reader become one.

The reader finds that he has a message to impart, a principle to establish, a rule of conduct to promulgate, and that he has done so in a logical, attractive manner which compels attention; and that to my mind is the test and measure of good writing.

Another view of Osler as an author is revealed in his occasional addresses and essays. In the two volumes before me—"Aequanimitas and Other Addresses" and "An Alabama Student and Other Biographical Addresses"—Osler's style in all its directness, strength and grace is shown in full measure.

In these volumes, as in other addresses not therein con-

tained, notably his farewell to his professional associates and friends in Maryland under the title "Unity, Peace and Concord," Osler exemplifies Buffon's dictum: "The style is the man himself."

Sir Thomas Watson in his memorial of Latham, whose "Lectures on Clinical Medicine" are examples of the best English style, says: "His letters are treasures of good sense, of lively and epigrammatic comments on men and things and of shrewd and weighty reflections, wise advice and affectionate greetings"; and this can be with great truth applied to the addresses and essays of Dr. Osler. Lively, epigrammatic, shrewd, weighty and affectionate are all terms which well suit my purpose, which reveal the man through his writing. "Talent alone cannot make a writer," says Emerson, "there must be a man behind the book, a personality which by birth and quality is pledged to the doctrines there set forth."

With Byron one "hates an author that's all author." In Osler's case the author is all man, and the man reflects himself in his work. It is an easy task for those who have had the pleasure and advantage of intimate association with him to invoke his presence when reading his addresses, as for example, "Internal Medicine as a Vocation," "Medicine in the Nineteenth Century," "The Hospital as a College" and "The Master Word in Medicine."

What, if any, are the secrets of Osler's style; upon what does it depend? The answer, I think, is simply a love for and thorough mastery of good literature and a message to convey full of high ideals. One William Harrison, writing in 1577, speaks of "an excellent vein of writing not beforetime regarded" which had become manifest in England. This he intimates is the result not only of a knowledge on the part of writers of their own tongue, but of an acquaintance with the Latin and Greek and often with French and Spanish.

This excellent vein of writing soon became the glory of the Elizabethan age. The development of higher ideals in English national life was rapidly followed, as well as fostered, by the great authors of the age of England's literary glory. Style, literary excellence, came to be recognized as desirable, and reached its highest manifestation. Back of it all, however, were the ideals which fostered and gave material for the expression of literary style. There was an atmosphere of a great elevation of ideals, public and private, and at the same time tangible objects of national ambition and glory. England was "contending in the cause of the world as well as her own" and there was an outburst of genius which found its counterpart in a smaller degree many years later when England was contending again the world-ambition of Napoleon.

Will a similar development follow the world's war out of which we are just emerging?

When a man who has ideals and honesty of purpose and has filled his mind with the productions of the master spirits of the ages feels the call to write or speak, a beauty of literary style almost inevitably results.

* Lectures on the Principles and Practice of Physic. By Thomas Watson, M. D., etc., London, 1843.

What were the Pierian springs from which Osler drank, from which he attained, as has been said of him, "a breadth of learning and a knowledge of general literature that astound one?"

I would place first the English Bible. How often either by direct quotation or paraphrase does one find in his addresses and essays sentences and phrases from this well-spring of good English.

Of a liberal knowledge of the classics abundant evidence is found and a ready ability to take text, and illustration as well, from mythology.

With the masters of the English tongue from the early dawn of English literature till the present he has clearly dwelt on terms of greatest intimacy.

That half hour devoted every day to communion with the minds of the past finds lessons reflected in writing, but never with any indication of servile copying. Osler's style is his own.

The last page of *Aequanimitas* has a list of books which Osler has called a Bed-side Library for Medical Students. This is: 1. Old and New Testament; 2. Shakespeare; 3. Montaigne; 4. Plutarch's Lives; 5. Marcus Aurelius; 6. Epicurus; 7. *Religio Medici*; 8. Don Quixote; 9. Emerson; 10. Oliver Wendell Holmes—Breakfast-Table Series.

John Brown, of Edinburgh (*Horae Subsecivae*, p. 400), gives a list which he commends to the medical student. These are "Shakespeare, Cervantes, Milton, Dryden, Pope, Cowper, Montaigne, Addison, Defoe, Goldsmith, Fielding, Scott, Lamb, Macaulay, Jeffrey, Sydney Smith, Helps and Thackeray." Brown's list has nearly twice as many names as that given by Osler, but in solid worth the shorter list outweighs the longer.

Dr. Osler's list fulfills in brief compass the requirements of a liberal education and presents to the reader examples of the best in literature.

Reference has already been made to the fact that Dr. Osler is reflected in his writings, that in the words of Taine "behind the document there was a man."

In this instance that man had for years exercised, as I have tried to show elsewhere, a singular and powerful influence on medical education, hospital methods and in binding together for harmonious action the members of his profession.

He had encouraged the study of medical history and biography and found time in the midst of duties, which might well have availed as an excuse from further intellectual labors, to contribute in large measure to these subjects.

Always, with no false note, his cry has been for scientific righteousness. He has had ideals and, as an idealist, he has done what he has himself said other idealists have often done, "gradually moulded to their will conditions the most adverse and hopeless."

All of this and much more is reflected in the text of Osler's writing, presented often in epigrammatic form, reinforced by text and example from many sources, enlivened by a humor that is irresistible.

No medical contributor to general literature since Holmes has possessed the saving sense of humor to the degree shown in Osler's writings and no one could have used it with greater discrimination or more certain effect.

Often when apparently writing in a most humorous vein he has been the most serious in his meaning, and how often and with what delicate touch does he expose some of our human faults and foibles. I yield to the temptation to quote here an illustration of that to which I have just referred. "Curious, odd compounds are these fellow-creatures, at whose mercy you will be; full of fads and eccentricities, of whims and fancies; but the more closely we study their little foibles of one sort and another in the inner life which we see, the more surely is the conviction borne in upon us of the likeness of their weaknesses to our own. The similarity would be intolerable if a happy egotism did not often render us forgetful of it. Hence the need of an infinite patience and an ever-tender charity toward these fellow creatures; have they not to exercise the same toward us?"

To Osler's style may be applied part of his own estimate of some of the older writers, Burton, Browne and Fuller: "A rare quaintness, a love of odd conceits and the faculty of apt illustration."

In his writings he reminds us of what he has said of Browne, "The charm of high thoughts clad in beautiful language may win some readers to a love of good literature; but beyond this is a still greater advantage . . . the *Religio* is full of the counsels of perfection."

So, too, is there with Osler a charm of high thoughts clad in beautiful language and always the "counsels of perfection."

Osler's literary work is yet unfinished, the three score years and ten which he has attained have but ripened his judgment and enlarged his field of vision. He has seen many of his ideals become realities. The stress of the great world war has pressed heavily upon him and brought to him a great sorrow. The iron has entered into his soul. His future work will bear the stamp of all these.

He has made his own estimate of the "princes of the blood" in literature from our profession. He places Sir Thomas Browne, Holmes and John Brown, of Edinburgh, in a group high in the circle.

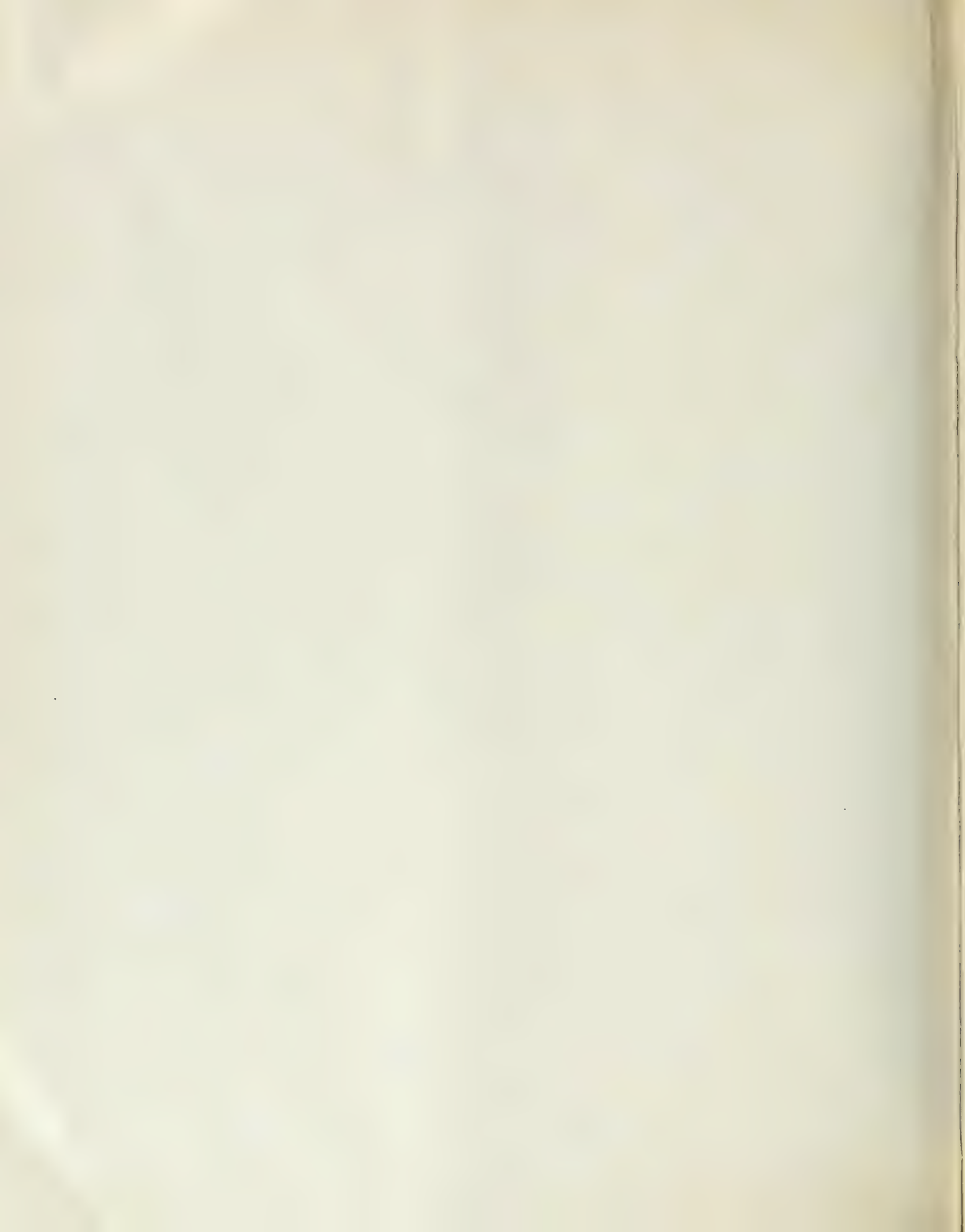
Osler possesses many things in common with these three in literary style and in literary excellence, and deserves a place in the same exalted fellowship.



(1) Respectability }
(2) Sobriety } in the faces of the
(3) Godliness } young Professors!

Im about 1900

M. Osler



BIBLIOGRAPHY

Sir William Osler's bibliography covers a period of 49 years (1870-1919). The 730 titles include both books and articles. Many of these are in the library of The Johns Hopkins Hospital and have added value as being personal gifts from the author.

1870

On Canadian diatomaceæ. *Canad. Naturalist*, Montreal, 1870, n. s., v. 142-151.

In his: Published Mem. & Communicat., Montreal, 1882, 8°.

[Collect. repr., 1872-1882, i, no. 1.]

1873

Action of certain reagents—atropia, physostigma and curare—on the colorless blood-corpuscles. *Quart. J. Micr. Sc.*, Lond., 1873, n. s., xlii, 307-309.

In his: Published Mem. & Communicat., Montreal, 1882, 8°.

[Collect. repr., 1872-1882, i, no. 2.]

1874

An account of certain organisms occurring in the liquor sanguinis. [Rep. by J. B. Sanderson.] *Proc. Roy. Soc.*, Lond., 1874, xxi, 391-398.

In his: Collect. repr., 1872-82, i, no. 3.

1875

Valedictory address to the graduates in medicine and surgery. McGill University. Canada M. & S. J., Montreal, 1874-75, iii, 433-438.

In his: Published Mem. & Communicat., Montreal, 1882, 8°.

[Collect. repr., 1872-82, i, no. 4.]

1876

Introductory remarks to, and synopsis of, practical course on institutes of medicine. Canada M. & S. J., Montreal, 1875-76, iv, 202-207.

On the pathology of miner's lung. Canada M. & S. J., Montreal, 1875-76, iv, 145-168.

In his: Collect. repr., 1872-82, i, no. 7.

Case of scarlatina miliaris. Canada M. & S. J., Montreal, 1875-76, iv, 49-54.

In his: Collect. repr., 1872-82, i, no. 5.

On the histology of leucocythemia. Canada M. & S. J., Montreal, 1875-76, iv, 439-477.

In his: Collect. repr., 1872-82, i, no. 6.

Clinical notes on small-pox. I. The initial rashes. II. Hemorrhagic small-pox. III. A form of hemorrhagic small-pox. Montreal, 1876. *Gazette P'tg House*, 35 p., 8°.

Also: Canada M. & S. J., Montreal, 1876-77, v, 241; 289.

In his: Published Mem. & Communicat., Montreal, 1882.

[Collect. repr., 1872-82, i, nos. 8, 9, 10.]

Trichina spiralis. Extract from a lecture on "Animal parasites and their relation to public health," being one of the Somerville lectures of the Natural history society. *Canad. J. M. Sc.*, Toronto, 1876, i, 134-135.

1877

Introductory lecture on the opening of the forty-fifth session of the medical faculty, McGill University, Oct. 1, 1877. Montreal, 1877. Dawson Bros., 19 p., 8°.

Also: Canada M. & S. J., Montreal, 1877-78, vi, 193-210.

In his: Published Mem. & Communicat., Montreal, 1882, 8°.

[Collect. repr., 1872-82, i, no. 14.]

Verminous bronchitis in dogs; read before the Montreal Veterinary Medical Association, March 29. *Veterinarian*, Lond., 1877, i, 387-397.

In his: Published Mem. & Communicat., Montreal, 1882, 8°.

[Collect. repr., 1872-82, i, no. 12.]

Beschaffenheit des Blutes und Knochenmarkes bei pernicioser Anämie. *Centralbl. f. d. med. Wissensch.*, Berl., 1877, xv, 498.

In his: Published Mem. & Communicat., Montreal, 1882, 8°.

[Collect. repr., 1872-82, i, no. 18.]

Osler, W., and Bell, J.: Case of progressive pernicious anæmia. Clinical report, by John Bell. Pathological report, with remarks, by William Osler. Montreal, 1877, Lovell Print. & Publ. Co., 12 p., 12°.

In his: Collect. repr., 1872-82, i, no. 16.

Osler, W., and Gardner, W.: Case of progressive pernicious anæmia (idiopathic of Addison). Canada M. & S. J., Montreal, 1876-77, v, 385-404.

In his: Collect. repr., 1872-82, i, no. 15.

Osler, W., and Gardner, W.: Ueber die Beschaffenheit des Blutes und Knochenmarkes in der progressiven perniciosen Anämie. *Centralbl. f. d. med. Wissensch.*, Berl., 1877, xv, 258-260.

In his: Published Mem. & Communicat., Montreal, 1882, 8°.

[Collect. repr., 1872-82, i, no. 17.]

1878

On the pathology of the so-called pig-typhoid. London, 1878, Baillière, Tindall & Cox, 20 p., 8°.

Vet. J. & Ann. Comp. Path., Lond., 1878, vi, 385-402.

In his: Published Mem. & Communicat., Montreal, 1882.

[Collect. repr., 1872-82, i, no. 20.]

Over-strain of the heart, as illustrated by a case of hypertrophy, dilatation and fatty degeneration of the heart, consequent upon prolonged muscular exertion. Montreal, 1878, *Gazette P'tg House*, 13 p., 8°.

Also: Canada M. & S. J., Montreal, 1877-78, vi, 385-395.

In his: Published Mem. & Communicat., Montreal, 1882, 8°.

[Collect. repr., 1872-82, i, no. 19.]

Phthitical cavities in left lung; gangrene of pulmonary tissue about one of them. Canada M. & S. J., Montreal, 1877-78, vi, 114.

Also: Montreal Gen. Hosp. Rep. (1876-77), 1878, i, 37.

Pleura. Small fibroid thickenings on visceral layer. Canada M. & S. J., Montreal, 1877-78, vi, 115-116.

Also: Montreal Gen. Hosp. Rep. (1876-77), 1878, i, 40-41.

Fracture of 1st and 2d ribs near vertebra, from direct violence; deep abscess of the neck; obliteration of subclavian artery; empyema. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 11-12.

Necrosis of tibia. Ulcerative endocarditis, pyæmic pneumonia. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 12-13.

Necrosis of femur, pyæmic pneumonia; abscesses in superficial muscles; pustular eruption on skin. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 13-14.

Primary cancer of bodies of 2d and 3d vertebra and heads of corresponding ribs on right side. Secondary masses in ribs, liver and brain. Chronic phthisis. Lobar pneumonia. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 14-16.

A case of hypertrophy and dilatation of the heart; no valvular or arterial disease; no chronic kidney affection; hydrothorax; pulmonary apoplexy; general venous stasis. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 16-20.

Aneurism of commencement of thoracic aorta, unsuspected during life; death from general tuberculosis. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 20-21.

Sacculated aneurism of ascending portion of arch of aorta; rupture into the right pleural sac. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 21.

Sacculated aneurism of aorta, at termination of the arch, unsuspected during life. Death from pneumonia. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 22.

Aneurism of hepatic artery. Right branch almost obliterated. Multiple abscesses in the liver. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 22-30.

Aneurismal dilatation of branches of pulmonary artery on the walls of phthitical cavities. Death from hæmoptysis. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 30.

Aneurism at second bifurcation of the right middle cerebral artery; rupture; extravasation of blood into the Sylvian fissure, and laceration of substance of the temporoparietal lobe; death in 36 hours. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 30-32.

- Ossification of greater portion of mucous membrane of trachea. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 32.
- Pneumonia of the upper lobe of the right lung; extensive meningeal inflammation. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 33-34.
- Almost entire hepatization of left lung; with small pneumonic area in right. Extensive diphtheritic colitis. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 34.
- Diabetes, phthisical cavity in right lung surrounded by hepatized tissue. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 34-35.
- Chronic phthisis, almost entire destruction of both lungs. Healthy portion involved in a pneumonia. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 35.
- Simple pneumonia of left lung, right-sided pleurisy. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 35.
- Pneumonia of right lung, uniform involvement of pleura covering it. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 35-37.
- Fibroid contraction and induration of entire right lung; cavity at apex; displacement of heart; hypertrophy with dilatation of right chambers. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 38-39.
- Chronic phthisis; perforation of lungs; pneumothorax; dermoid cyst of right ovary. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 39-40.
- Epithelioma of right side of tongue, extending from base to near the apex. Removal of organ with galvanic écraseur. Suppuration beneath cervical fascia. Pyæmia. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 41-42.
- Chronic phthisis. Miliary tubercles in lungs and pharynx. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 42-43.
- Cancer of the cardiac orifice, involving the œsophagus. Secondary masses in other parts of the organ. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 43-44.
- Medullary cancer, involving the pyloric zone of the stomach; perforation, peritonitis. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 44.
- Passage of two feet of the ileum through a loop attached to the sigmoid flexure. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 45.
- Round ulcer of duodenum. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 45-46.
- Perforation of typhoid ulcer during convalescence, owing to an indiscretion in diet. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 46.
- Perforation of a deep ulcer at end of second week. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 46-47.
- Typhoid fever. Perforation. Peritonitis. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 47.
- Four round ulcers in the ileum. Peyer's patches not generally involved. Slight hypostatic pneumonia. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 48.
- Slight swelling of Peyer's glands, only one small spot of ulceration. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 48.
- Round ulcer of cæcum, perforation, general peritonitis. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 49.
- Abscesses in the mesentery. Suppuration of portal vein. Empyema. Perforation of appendix, general peritonitis. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 51.
- Acute tubercular inflammation of the peritoneum. Small caseous mass in left lung. Right-sided pleurisy. General hyperplasia of the bone marrow. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 52-56.
- Cirrhosis of liver, with enlargement; jaundice; no ascites; delirium tremens (?) ; erysipelas of the head. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 56-60.
Also: Canada M. & S. J., Montreal, 1877-78, vi, 249-253.
- Syphilitic ulceration of left frontal bone; large node on left tibia; gummatous in liver. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 60-61.
Also: Canada M. & S. J., Montreal, 1877-78, vi, 253.
- Primary cancer of the liver; ascites; jaundice; secondary mass in tail of pancreas; small secondary nodules in kidneys. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 61-64.
Also: Canada M. & S. J., Montreal, 1877-78, vi, 254-256.
- Cancer of neck of the gall-bladder and lymphatic glands in the portal fissure; compression of the hepatic ducts; secondary masses in liver; enormous distension of gall-bladder and hæmorrhage into it; gall-stones. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 64-65.
- Extensive abscesses in the mesentery, following typhoid fever. Suppuration of the portal vein and its branches in the liver. Empyema. Perforation of the appendix vermiformis; peritonitis; miliary tubercles in lungs. Amyloid degeneration of spleen, liver, and mucous membrane of small intestine. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 65-71.
- Tuberculous disease of right kidney, pelvis, ureter and bladder. Tubercles in left kidney and lungs. Perforation of tuberculous ulcer in bladder. Peritonitis. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 72-73.
- Old scrofulous disease of right kidney, which is converted into cysts. Recent affection of the left. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 73-74.
- Old disease of the right kidney, which is converted into five or six cysts, filled with a putty-like material. Extensive tuberculous disease of the organ. Miliary tubercles in lungs. Albuminoid spleen. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 74-75.
- Suppuration about right kidney. Pyæmic abscesses in elbows, ankles and anterior mediastinum. Peritonitis. Pleurisy. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 75-76.
- Stone in the bladder. Prostatic tumors around the urethral orifice. Ulceration on mucous membrane. Pyelitis; ulceration of apices of renal pyramids. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 76-77.
- Epithelioma of cervix; obstruction of the canal; dilatation of the uterine cavity. Pyometra. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 77-78.
- Dermoid or piliferous cyst of right ovary. Chronic phthisis. Pneumothorax. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 78-79.
- Small cavity and caseous masses in lung. General tuberculosis. Meninges of brain unaffected; central softening. Spinal meninges extensively involved. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 79-81.
- Meningeal affection slight. Ventricles distended, walls soft. Very few miliary tubercles in the organs. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 81-82.
- Meningeal affection very extensive on the cortex, slight at the base. Ventricles large, walls not soft. Large caseous mass in left lung. Miliary tubercles in lungs and on peritoneum. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 82-83.
- Slight meningeal inflammation. One caseous mass and a few tubercles in lungs. Old morbus coxæ. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 84.
- Profound anæmia without discoverable lesion. Fatty degeneration of organs. Hyperplasia of bone-marrow. Montreal Gen. Hosp. Path. Rep. (1876-77), 1878, i, 84-97.
- Ueber die Entwicklung von Blutkörperchen im Knochenmark bei perniziöser Anämie. [Berlin, 1878, L. Schumacher.] Centralbl. f. d. med. Wissensch., Berl., 1878, xvi, 465-467.
In his: Published Mem. & Communicat., Montreal, 1882, 8°.
[Collect. repr., 1872-82, i, no. 21.]
- Osler, W., and Ross, G.: Aneurism of hepatic artery; multiple abscesses of the liver. Canada M. & S. J., Montreal, 1877-78, vi, 1-12.
In his: Collect. repr., 1872-82, i, no. 13.

- Case of obliteration of vena cava inferior, with great stenosis of orifices of hepatic veins. J. Anat. & Physiol., Lond., 1878-79, xiii, 291-304.
In his: Collect. repr., 1872-82, i, no. 24.
- Two cases of rare kidney tumors. Canada M. Rec., Montreal, 1879, vii, 164.

Miner's phthisis (Rep. by R. Dawson). Canada M. & S. J., Montreal, 1878-79, vii, 452-454.
Also: Montreal Gen. Hosp. Rep., 1880, i, 297-299.

Acute Bright's disease in a child; remarkable persistence of blood-corpuses and casts in the urine after disappearance of albumin. (Rep. by A. Henderson.) Canada M. & S. J., Montreal, 1878-79, vii, 455.

Aphasia, with right-sided hemiplegia, coming on fifteen days after delivery. [Rep. by D. Mignault.] Canada M. & S. J., Montreal, 1878-79, vii, 492-493.

Acute rheumatism treated with salicylate of soda. Delirium apparently caused by the remedy. [Rep. by B. E. Mackenzie.] Canada M. & S. J., Montreal, 1878-79, vii, 493-494.

Cohnheim's theory of tumors. Transl. and condensed from vol. I of his Vorlesungen über allgemeine Pathologie (Lectures upon general pathology). By Dr. Osler. Canada M. & S. J., Montreal, 1878-79, vii, 337-347; 398-408.

1880

Concussion of brain; temporary hemiplegia; general convulsions; rapid recovery. [Rep. by Imrie.] Canada M. & S. J., Montreal, 1879-80, viii, 8.

Aggravated stuttering, following fall on the head. Canada M. & S. J., Montreal, 1879-80, viii, 9.

Extreme irregularity of the heart. [Rep. by E. J. Rogers.] Canada M. & S. J., Montreal, 1879-80, viii, 9.

Chronic pleurisy; flattening of sides of chest. Canada M. & S. J., Montreal, 1879-80, viii, 109-111.

Croup or diphtheria; which? Canada M. & S. J., Montreal, 1879-80, viii, 207-211.
In his: Collect. repr., 1872-82, i, no. 23.

Three cases of brain disease. Canada M. & S. J., Montreal, 1879-80, viii, 295; 346.

Anomalous case of pyæmia; suppuration about tissues in left inferior carotid triangle; pyæmic abscess beneath tensor vaginæ femoris; pyæmic infarcts in the lungs; septic pleurisy. Canada M. & S. J., Montreal, 1879-80, viii, 544-548.

Catalogue of a series of specimens illustrative of the morbid anatomy of the brain and spinal cord. Exhibited at Ottawa Meeting of Canada Medical Association, Sept. 1 and 2, 1880.

Case of congenital and progressive hypertrophy of the right upper extremity. J. Anat. & Physiol., Lond., 1879-80, xiv, 10-12.
In his: Collect. repr., 1872-82, i, no. 25.

Two cases of striated myo-sarcoma of the kidney. J. Anat. & Physiol., Lond., 1879-80, xiv, 229-233.
In his: Collect. repr., 1872-82, i, no. 26.

Cases of cardiac abnormalities. Montreal Gen. Hosp. Rep., 1880, i, 177-192.
In his: Collect. repr., 1872-82, i, no. 27.

On the condition of fusion of two segments of the semilunar valves. Montreal Gen. Hosp. Rep., 1880, i, 233-242.
In his: Collect. repr., 1872-82, i, no. 28.

Wound of the central part of the 1st and 2d frontal convolutions on left side. Montreal Gen. Hosp. Rep., 1880, i, 257-258.

Bullet wound of right frontal lobe; entire absence of cerebral symptoms. Montreal Gen. Hosp. Rep., 1880, i, 258-260.

Cases of aneurism of the aorta. Montreal Gen. Hosp. Rep., 1880, i, 260-265.

Aneurism of innominate-rupture of sacular dilatation of aorta into pericardium. Montreal Gen. Hosp. Rep., 1880, i, 265-266.

Aneurism of splenic artery; perforation into transverse colon. Montreal Gen. Hosp. Rep., 1880, i, 266-268.

Small aneurism of renal artery. Montreal Gen. Hosp. Rep., 1880, i, 268.

Four cases of intracranial aneurism. Montreal Gen. Hosp. Rep., 1880, i, 268-275.

Aneurisms of branches of pulmonary artery on wall of cavities; hæmoptysis in chronic phthisis. Montreal Gen. Hosp. Rep., 1880, i, 275-276.

Two cases of hypertrophy of the heart. Montreal Gen. Hosp. Rep., 1880, i, 276-282.

Perforation of pulmonary artery by ulcer of left bronchus; sudden death from hæmoptysis; chronic bronchitis, emphysema, phthisis. Montreal Gen. Hosp. Rep., 1880, i, 282-283.

Instance of four pulmonary valves. Montreal Gen. Hosp. Rep., 1880, i, 284.

Bayonet wound of left subclavian artery at its origin. Montreal Gen. Hosp. Rep., 1880, i, 284.

Fatty degeneration of heart in diphtheria; sudden death on the thirteenth day. Montreal Gen. Hosp. Rep., 1880, i, 285.

Two cases of thrombosis of pulmonary artery. Montreal Gen. Hosp. Rep., 1880, i, 285-287.

Thrombosis of branches of right pulmonary artery. Montreal Gen. Hosp. Rep., 1880, i, 287-290.

Edema of right lung; hydrothorax of left pleura; contracted kidneys. Montreal Gen. Hosp. Rep., 1880, i, 290-291.

Edema of left lung; morphia poisoning. Montreal Gen. Hosp. Rep., 1880, i, 291-292.

Pneumonia; ulcerative endocarditis; meningitis. Montreal Gen. Hosp. Rep., 1880, i, 292-295.

Pneumonic phthisis. Montreal Gen. Hosp. Rep., 1880, i, 295-297.

Note on the occurrence of membrane in the trachea and bronchi in diphtheria. Montreal Gen. Hosp. Rep., 1880, i, 299-300.

Foreign body in œsophagus; ulceration; perforation; retro-pharyngeal and œsophageal abscess. Montreal Gen. Hosp. Rep., 1880, i, 300-301.

Three cases of cancer of the stomach. Montreal Gen. Hosp. Rep., 1880, i, 301-302.

Three cases of ulcer of the stomach. Montreal Gen. Hosp. Rep., 1880, i, 304-306.

Three cases of simple ulcer of duodenum. Montreal Gen. Hosp. Rep., 1880, i, 306-311.

Typhoid fever; rapidly fatal, with nervous symptoms. Montreal Gen. Hosp. Rep., 1880, i, 311-312.

Perforation of appendix vermiformis; circumscribed abscess; perforation of ileum; hæmorrhage from bowels. Montreal Gen. Hosp. Rep., 1880, i, 313-314.

Liver; hydatid cyst. Montreal Gen. Hosp. Rep., 1880, i, 314-316.

Primary cancer of liver. Montreal Gen. Hosp. Rep., 1880, i, 316-317.

Cirrhosis of liver; collateral circulation by means of an enlarged umbilical vein; death from pneumonia. Montreal Gen. Hosp. Rep., 1880, i, 317-318.

Pylephlebitis. Montreal Gen. Hosp. Rep., 1880, i, 318-321.

Extensive scald of thorax; pneumonia; numerous spots of fatty degeneration in kidneys. Montreal Gen. Hosp. Rep., 1880, i, 321-322.

Small contracted kidneys; left organ affected to an unusual degree; right only involved in the lower part; hypertrophy of heart. Montreal Gen. Hosp. Rep., 1880, i, 322-324.

Large cirrhotic kidneys (congested); hypertrophy of heart; apoplexy. Montreal Gen. Hosp. Rep., 1880, i, 324-325.

Sarcoma of left kidney. Montreal Gen. Hosp. Rep., 1880, i, 325-328.

Dermoid of ovary; ulcerative colitis. Montreal Gen. Hosp. Rep., 1880, i, 328-329.

Cancer of neck of uterus; constriction of right ureter; pyonephrosis. Montreal Gen. Hosp. Rep., 1880, i, 329-331.

Ruptured follicle in right ovary; peritonitis. Montreal Gen. Hosp. Rep., 1880, i, 331-333.

Extra-uterine (abdominal) pregnancy. Montreal Gen. Hosp. Rep., 1880, i, 333-335.

Cryptorchidismus. Montreal Gen. Hosp. Rep., 1880, i, 335-336.

Medullary sarcoma of axillary glands; secondary masses in heart, lungs, stomach, intestines, liver, spleen, kidneys, suprarenal capsules, and pancreas. Montreal Gen. Hosp. Rep., 1880, i, 336-339.

Sarcoma of retro-peritoneal glands; Lobstein cancer. Montreal Gen. Hosp. Rep., 1880, i, 339-340.

Lympho-sarcoma of deep cervical glands, involving the thyroid and simulating goitre. Montreal Gen. Hosp. Rep., 1880, i, 340-342.

On Giacomini's method of preserving the brain. *Med. Rec., N. Y.*, 1880, xvii, 315-316.

On the systolic brain murmur of children. *Boston M. & S. J.*, 1880, clii, 29-30.

In his: Collect. repr., 1872-82, i, no. 30.

On heredity in progressive muscular atrophy as illustrated in the Farr family of Vermont. *Arch. Med., N. Y.*, 1880, iv, 316-320.

In his: Collect. repr., 1872-82, i, no. 33.

On a remarkable heart-murmur, heard at a distance from chest-wall. *Med. Times & Gaz., Lond.*, 1880, ii, 432.

In his: Collect. repr., 1872-82, i, no. 34.

Lympho-sarcoma of deep cervical glands, involving the thyroid and simulating goitre. *Montreal Gen. Hosp. Rep.*, 1880, i, 340-342.

Montreal General Hospital. Pathological reports. 1. (1876-77); 2. (1877-79), Montreal, 1878-80. (2. report repr. from: *Montreal Gen. Hosp. Rep., Clin. & Path.*, 1880, i.)

1 and 2 also in *his:* Published Mem. & Communicat., Montreal, 1882.

[Collect. repr., 1872-82, i, nos. 22 & 29.]

Osler, W., ed. Montreal General Hospital. Reports, clinical and pathological, by the medical staff. v. i, Montreal, 1880, Dawson Brothers, 390 p., 8°.

1881

On some points in the etiology and pathology of ulcerative endocarditis. *Lond.*, 1881, J. W. Kolckmann, 8 p., 8°.

Tr. Internat. M. Cong., 7. sess., Lond., 1881, i, 341-346.

In his: Collect. repr., 1882-92, ii, no. 44.

Renal cirrhosis; with special reference to its latency and to sudden, fatal manifestations occurring in its course. *Toronto*, 1881, Dudley & Barnes, 13 p., 8°.

Canada Lancet, Toronto, 1880, xiii, 353-359.

In his: Collect. repr., 1872-82, i, no. 42.

On some of the effects of the chronic impaction of gallstones in the bile-passages, and on the "fièvre intermittente hépatique" of Charcot. *London*, 1881, Pardon & Sons, 15 p., 12°.

Med. Times & Gaz., Lond., 1881, ii, 111-114.

In his: Collect. repr., 1872-82, i, no. 41.

Cases of insular sclerosis. *Canada M. & S. J.*, Montreal, 1880-81, ix, 1-11.

In his: Collect. repr., 1872-82, i, no. 31.

Case of medullary neuroma of the brain. *J. Anat. & Physiol.*, Lond., 1880-81, xv, 217-225.

In his: Collect. repr., 1872-82, i, no. 35.

Retro-peritoneal cancer. *Canada M. & S. J.*, Montreal, 1880-81, ix, 161.

Brief description of the new physiological laboratory, McGill College. *Canada M. & S. J.*, Montreal, 1880-81, ix, 198-201.

Cases of Hodgkin's disease. *Canada M. & S. J.*, Montreal, 1880-81, ix, 385-397.

In his: Collect. repr., 1872-82, i, no. 37.

Clinical lecture on a case of fibroid phthisis. Delivered at the Montreal General Hospital in the summer session course, May 10, 1881. *Canada M. & S. J.*, Montreal, 1880-81, ix, 641-650.

In his: Collect. repr., 1872-82, i, no. 40.

Notes of the second demonstration in the morbid anatomy course in McGill College. *Canad. J. M. Sc.*, Toronto, 1881, vi, 350-353.

On delayed resolution in pneumonia. *Canada Lancet*, Toronto, 1880-81, xiii, 99-103.

In his: Collect. repr., 1872-82, i, no. 32.

Clinical lecture on idiopathic or pernicious anæmia. *Canad. J. M. Sc.*, Toronto, 1881, vi, 135-141.

In his: Collect. repr., 1872-82, i, no. 39.

Infectious (so-called ulcerative) endocarditis. *Arch. Med., N. Y.*, 1881, v, 44-68.

In his: Collect. repr., 1872-82, no. 36.

Ulcerative endocarditis. *Bull. N. York. Path. Soc.*, 1881, 2. s., i, 29-33.

Notes on intestinal diverticula. *Ann. Anat. & Surg.*, Brooklyn, N. Y., 1881, iv, 202-207.

In his: Collect. repr., 1872-82, i, no. 43.

1882

Published memoirs and communications. (To Jan. 1, 1882), *Montreal*, 1882, 8°.

Collected reprints. First series, 1872-1882, Montreal, 1882, 8°.

["Published memoirs and communications" the same as "Collected reprints, First series."]

Clinical remarks on cases of inherited syphilis. *Canada M. & S. J.*, Montreal, 1881-82, x, 588-592.

Clinical remarks on leucocythemia. *Canada M. & S. J.*, Montreal, 1881-82, x, 719-727.

On the brains of criminals. With a description of the brains of two murderers. *Canada M. & S. J.*, Montreal, 1881-82, x, 385-398.

In his: Collect. repr., 1882-92, ii, no. 45.

Case of obliteration of the portal vein (pyelephlebitis adhesiva). *J. Anat. & Physiol.*, Lond., 1881-82, xvi, 208-216.

In his: Collect. repr., 1882-92, ii, no. 46.

Ueber den driften Formbestandteil des Blutes. *Centralbl. f. d. med. Wissensch.*, Berl., 1882, xx, 529-531.

In his: Collect. repr., 1882-92, ii, no. 47.

Summer session clinics. No. 1. Cases of inherited syphilis. No. 2. Acute Bright's disease. Nos. 3-4. Pneumonia. No. 5. Leucocythemia. *Montreal*, 1882, 44 p., 8°.

In his: Collect. repr., 1882-92, ii, no. 48.

A clinical lecture on empyema and its antiseptic treatment. *Med. News*, Phila., 1882, xli, 113-115.

In his: Collect. repr., 1882-92, ii, no. 50.

Uræmic delirium and coma at a very early stage of interstitial nephritis. *Arch. Med., N. Y.*, 1882, vii, 213-215.

In his: Collect. repr., 1882-92, ii, no. 51.

On certain parasites in the blood of the frog. *Canad. Naturalist*, Montreal, 1882, x, 406-410.

In his: Collect. repr., 1882-92, ii, no. 52.

On Canadian fresh-water polyzoa. *Canad. Naturalist*, Montreal, 1882, x, 399-405.

In his: Collect. repr., 1882-92, ii, no. 53.

On echinococcus disease in America. *Am. J. M. Sc.*, Phila., 1882, n. s., lxxxiv, 475-480.

In his: Collect. repr., 1882-92, ii, no. 62.

Atheromatous plate and ulcers on arch of aorta. *Med. News*, Phila., 1882, xli, 249.

Atheromatous abscess and aneurism of the right iliac artery; general atheroma. *Med. News*, Phila., 1882, xli, 250.

Fatty diarrhœa. *Med. News*, Phila., 1882, xli, 580.

Tapping the gall-bladder. *Med. News*, Phila., 1882, xli, 580.

Hæmatemesis in chronic enlargement of the spleen. *Med. News*, Phila., 1882, xli, 581.

Notes on cells containing red blood-corpuscles. *Lancet*, Lond., 1882, i, 181.

1883

Cancer of ascending colon; extensive secondary growths in liver. *Canada M. & S. J.*, Montreal, 1882-83, xi, 28.

Obstinate quotidian ague. *Canada M. & S. J.*, Montreal, 1882-83, xi, 29.

Clinical note on hæmatemesis in chronic splenic tumour. *Canada M. & S. J.*, Montreal, 1882-83, xi, 267-270.

Also: *Canada M. Rec.*, Montreal, 1882-83, xi, 30.

Erosion of internal carotid in cavernous sinus six weeks after a blow on the head; fatal hæmorrhage from the nose. *Canada M. & S. J.*, Montreal, 1882-83, xi, 357.

Aneurism of anterior communicating artery. *Canada M. Rec.*, Montreal, 1882-83, xi, 133.

Empyema discharging through lung; recovery. *Canada M. Rec.*, Montreal, 1882-83, xi, 223.

Aneurism of the anterior cerebral artery. *Canada M. Rec.*, Montreal, 1882-83, xi, 241.

Clinical remarks on a case of Hodgkin's disease. *Canada M. & S. J.*, Montreal, 1882-83, xi, 712-717.

In his: Collect. repr., 1882-92, ii, no. 55.

Preataxic tabes dorsalis. A clinical lecture delivered during the summer session of the McGill Medical Faculty. *Med. News*, Phila., 1883, xliii, 197-199.

In his: Collect. repr., 1882-92, ii, no. 56.

The third corpuscle of the blood. *Med. News, Phila.*, 1883, xliii, 701-702.

In his: Collect. repr., 1882-92, ii, no. 57.

On some natural modes of cure in empyema. A clinical lecture delivered during the summer session of the McGill Medical Faculty, June 20, 1883. *Med. Rec.*, N. Y., 1883, xxiv, 429-431.

In his: Collect. repr., 1882-92, ii, no. 58.

Report on the brains of Richards and O'Rourke. *Canada M. & S. J.*, Montreal, 1882-83, xi, 461-466.

In his: Collect. repr., 1882-92, ii, no. 59.

Secondary myeloid disease of pleura and lung. *Illust. M. & S.*, N. Y., 1883, ii, 117.

Clinical remarks on the nephritis of pregnancy. *Canad. Pract.*, Toronto, 1883, viii, 133-137.

Thrombosis and embolism of the superior mesenteric artery. *Med. News, Phila.*, 1883, xliii, 693.

Scirrhus of pancreas: secondary colloid of lungs. *Med. News, Phila.*, 1883, xliii, 694.

Osler, W., and Clement, A. W. Cestode tuberculosis. A successful experiment in producing it in the calf. *Am. Vet. Rev.*, N. Y., 1882-83, vi, 6-10.

In his: Collect. repr., 1882-92, ii, no. 49.

Osler, W., and Clement, A. W. An investigation into the parasites in the pork supply of Montreal. *Montreal, 1883, Gazette Printing Co.*, 14 p., 8°.

Also: Canada M. & S. J., Montreal, 1882-83, xi, 325-336.

In his: Collect. repr., 1882-92, ii, no. 54.

1884

Ovarian cysts in an infant. *Canada M. Rec.*, Montreal, 1883-84, xii, 52.

Fibro-glioma of upper end of ascending frontal gyrus; Jacksonian epilepsy of fourteen years' standing; the leg-centre. *Canada M. Rec.*, Montreal, 1883-84, xii, 82.

Aneurism of aorta: rupture into left bronchus. *Canada M. Rec.*, Montreal, 1883-84, xii, 98.

Cases of dysentery. *Canada M. & S. J.*, 1883-84 xii, 330-333.

Syphilitic caries of inner table of skull; great thickening of calvaria; compression and deformity of the brain. *Med. News, Phila.*, 1884, xliiv, 25.

Also: Canada M. & S. J., Montreal, 1883-84, xii, 351.

Also: Canada M. Rec., Montreal, 1883-84, xii, 78.

1885

Remarks on clinical cases. *Canada M. & S. J.*, Montreal, 1884-85, xliii, 328-333.

In his: Collect. repr., 1882-92, ii, no. 60.

A contribution to Jacksonian epilepsy and the situation of the leg centre. *Am. J. M. Sc.*, Phila., 1885, n. s., lxxix, 31-37.

In his: Collect. repr., 1882-92, ii, no. 61.

The Gulstonian lectures on malignant endocarditis. Delivered at the Royal College of Physicians of London, March, 1885. London, 1885, 31 p., 8°.

Also: Brit. M. J., Lond., 1885, i, 467-470; 522; 577.

Also: Lancet, Lond., 1885, i, 415; 459; 505.

Also: Med. News, Phila., 1885, xliiv, 309-313; 337; 365.

In his: Collect. repr., 1882-92, ii, no. 63.

Notes on the morbid anatomy of pneumonia. *Canada M. & S. J.*, Montreal, 1884-85, xliii, 596-605.

In his: Collect. repr., 1882-92, ii, no. 64.

Notes on the morbid anatomy of pneumonia. *Canada M. & S. J.*, Montreal, 1884-85, xliii, 596-605.

Specimen of aneurism of the aorta with rupture into the trachea in two places, and perforation of the œsophagus. *Boston M. & S. J.*, 1885, cxli, 480.

Du développement de la profession médicale en Canada. *Union méd. du Canada, Montreal*, 1885, xiv, 481-489; 529-539.

1886

The structure of certain gliomata. *Phila. M. Times*, 1885-86, xvi, 394.

Also: Med. News, Phila., 1886, xlviii, 220.

Aneurism of the cerebral arteries. *Canada M. & S. J.*, Montreal, 1885-86, xiv, 660-666.

In his: Collect. repr., 1882-92, ii, no. 75.

A case of retro-peritoneal spindle-celled sarcoma with extensive thrombotic and hemorrhagic changes. *Med. News, Phila.*, 1886, xlviii, 263.

In his: Collect. repr., 1882-92, ii, no. 69.

Spindle-celled sarcoma of the retro-peritoneum with extensive thrombotic degeneration. *N. York M. J.*, 1886, xliii, 136.

Also: Maryland M. J., Balt., 1885-86, xiv, 269-271.

Also: Semi-Month. J. Proc. Path. Soc., Phila., Wilmington, 1886, i, 3.

Cartwright lectures. Delivered before the Association of Physicians and Surgeons, New York, March 23, 27, 30, 1886. On certain problems of the blood corpuscles. 1. The blood plaque or third corpuscle. 2. Degeneration and regeneration of the corpuscles. 3. The relation of the corpuscles to coagulation. *Phila.*, 1886, 55 p., 8°.

Also: Med. News, Phila., 1886, xlviii, 365; 393; 421.

Also: Med. Rec., N. Y., 1886, xxix, 377; 405; 433.

Also: N. York M. J., 1886, xliii, 341; 369; 397.

In his: Collect. repr., 1882-92, ii, no. 71.

Abstracts of the Cartwright lectures on certain problems in the physiology of the blood-corpuscles. *Brit. M. J.*, Lond., 1886, i, 807; 861.

The bicuspid condition of the aortic valves. *Tr. Ass. Am. Physicians, Phila.*, 1886, i, 185-192.

In his: Collect. repr., 1882-92, ii, no. 72.

On the use of arsenic in certain forms of anæmia. *Detroit*, 1886, G. S. Davis, 14 p., 8°.

Also: Therap. Gaz., Detroit, 1886, 3. s., ii, 741-746.

Also: Coll. & Clin. Rec., Phila., 1886, vii, 231-233.

In his: Collect. repr., 1882-92, ii, no. 73.

Embolism of right middle cerebral artery; chronic nephritis. *Med. News, Phila.*, 1886, xlix, 554.

On the treatment of pleurisy with effusion by Hay's method. [Abstr.] *Med. News, Phila.*, 1886, xlix, 645.

Pypneumothorax subphrenicus. *Semi-Month. J. Proc. Path. Soc.*, Phila., Wilmington, 1886, i, 5.

The relation of the corpuscles to coagulation and thrombosis. *Brit. M. J.*, Lond., 1886, i, 917-919.

Osler, W., and Henry, F. P. Atrophy of the stomach, with the clinical features of progressive pernicious anæmia. *Am. J. M. Sc.*, Phila., 1886, n. s., xci, 498-511.

In his: Collect. repr., 1882-92, ii, no. 70.

Osler, W., and Hughes, W. Hemorrhagic pancreatitis with swelling of semilunar ganglia and Pacinian corpuscles. *Semi-Month. J. Proc. Path. Soc.*, Phila., Wilmington, 1886, i, 7.

1887

Extracts from Pathological Society of Philadelphia, 1885-1887, xlii-xliii, Philadelphia [1887], 69 p., 8°.

Duodenal ulcer; clinical and anatomical considerations based on nine cases. *Canada M. & S. J.*, Montreal, 1886-87, xv, 449-461.

In his: Collect. repr., 1882-92, ii, no. 74.

An address on the hamatozoa of malaria. *Brit. M. J.*, Lond., 1887, i, 556-562.

In his: Collect. repr., 1882-92, ii, no. 76.

Antifebrin. *Therap. Gaz.*, Detroit, 1887, 3. s., iii, 163-167.

In his: Collect. repr., 1882-92, ii, no. 77.

The cardiac relations of chorea. *Am. J. M. Sc.*, Phila., 1887, n. s., xciv, 371-386.

In his: Collect. repr., 1882-92, ii, no. 78.

BIBLIOGRAPHY COMPILED BY

MINNIE WRIGHT BLOGG

LIBRARIAN, JOHNS HOPKINS HOSPITAL

Notes on hæmorrhagic infarction. Boston M. & S. J., 1887, cxvii, 325-328.

Also: Tr. Ass. Am. Physicians, Phila., 1887, ii, 133-141.
In his: Collect. repr., 1882-92, ii, no. 79.

On the general etiology and symptoms of chorea, based on the records of 410 cases at the Infirmary for Nervous Diseases, Philadelphia. Med. News, Phila., 1887, li, 437; 465.
In his: Collect. repr., 1882-92, ii, no. 80.

Case of cholesteatoma of floor of third ventricle and of the infundibulum. J. Nerv. & Ment. Dis., N. Y., 1887, xiv, 657-673.
In his: Collect. repr., 1882-92, ii, no. 81.

1888

Hereditary angio-neurotic edema. Am. J. M. Sc., Phila., 1888, n. s., xcv, 362-367.
In his: Collect. repr., 1882-92, ii, no. 82.

Note on nitro-glycerine in epilepsy. J. Nerv. & Ment. Dis., N. Y., 1888, n. s., xlii, 38-39.
In his: Collect. repr., 1882-92, ii, no. 83.

The diagnosis of small-pox. Med. Standard, Chicago, 1888, iii, 97.
In his: Collect. repr., 1882-92, ii, no. 84.

Glioma of the medulla oblongata. J. Nerv. & Ment. Dis., N. Y., 1888, n. s., xlii, 172-176.
In his: Collect. repr., 1882-92, ii, no. 85.

The cerebral palsies of children. Med. News, Phila., 1888, liii, 29; 57; 85; 113; 141.
In his: Collect. repr., 1882-92, ii, no. 86.

Cases of diseases of the appendix and cæcum. Med. & Surg. Reporter, Phila., 1888, lix, 419-422.
In his: Collect. repr., 1882-92, ii, no. 87.

Puerperal anæmia, and its treatment with arsenic. Boston M. & S. J., 1888, cxix, 454.
Also: North Car. M. J., Wilmington, 1888, xxii, 359-363.
In his: Collect. repr., 1882-92, ii, no. 88.

On the diagnosis of duodenal ulcer. Med. Rec., N. Y., 1888, xxxiv, 609-610.
In his: Collect. repr., 1882-92, ii, no. 89.

Note on pachymeningitis hemorrhagica. J. Nerv. & Ment. Dis., N. Y., 1888, n. s., xlii, 608-612.
Also: Med. News, Phila., 1888, liii, 563-565.
In his: Collect. repr., 1882-92, ii, no. 90.

On lesions of the conus medullaris and cauda equina, and on the situation of the aho-vesical centre in man. Med. News, Phila., 1888, liii, 669-671.
In his: Collect. repr., 1882-92, ii, no. 91.

On a form of purpura associated with articular, gastro-intestinal, and renal symptoms. N. York M. J., 1888, xlviii, 675-677.
In his: Collect. repr., 1882-92, ii, no. 92.

An accouchement in a railway closet. Canada M. & S. J., Montreal, 1888, xvi, 377.
Also: Med. Rec., N. Y., 1888, xxxiii, 97.

Pulsating pleurisy. Tr. Ass. Am. Physicians, Phila., 1888, iii, 330-338.
Also: Am. J. M. Sc., Phila., 1889, n. s., xcvi, 43-50.
In his: Collect. repr., 1882-92, ii, no. 95.

Enlargement and congestion of the right arm following exercise of its muscles. Med. News, Phila., 1888, lii, 330.
Also: J. Nerv. & Ment. Dis., N. Y., 1888, n. s., xlii, 246-248.

A case of local syncope and asphyxia of the fingers. J. Nerv. & Ment. Dis., N. Y., 1888, n. s., xlii, 207-208.

1889

The cerebral palsies of children; a clinical study from the Infirmary for Nervous Diseases, Philadelphia. Phila., 1889, P. Blakiston, Son & Co., 111 p. 8°.

Aequanimitas. Valedictory remarks to the graduates in medicine of the University of Pennsylvania, May 1, 1889. Phila., 1889, W. F. Fell & Co., 10 p., 8°.
In his: Collect. repr., 1882-92, ii, no. 97.

The mortality of pneumonia. Phila., 1889, 7 p. 8°.
Also: Univ. M. Mag., Phila., 1888-89, i, 77-82.
In his: Collect. repr., 1882-92, ii, no. 93.

Two cases of ulcerative endocarditis. Univ. M. Mag., Phila., 1888-89, i, 31-32.

The mortality in pneumonia. Univ. M. Mag., Phila., 1888-89, i, 225.
Cancer of the stomach, extreme mobility of tumor. Univ. M. Mag., Phila., 1888-89, i, 368-370.

On the conditions of the brain suitable for operative interference. [Abstr.] Univ. M. Mag., Phila., 1888-89, i, 465-468.
Also: Canad. Pract., Toronto, 1889, xiv, 165-167.

On certain symptoms of floating kidney. Montreal M. J., 1888-9, xvii, 416-418.

The anatomical tubercle. Montreal M. J., 1888-9, xvii, 418.

Aortic aneurism; hemorrhage from the lungs. Phila. M. Times, 1888-9, xix, 223.

Typhlitis and appendicitis. Canada Lancet, Toronto, 1888-9, xxi, 193-196.

On phagocytes. An address before the Alumni Association of Bellevue Hospital, New York, delivered April 3, 1889. Med. News, Phila., 1889, liv, 393; 421.
Also: Med. Rec., N. Y., 1889, xxxv, 393-399.
Also: N. York M. J., 1889, xlix, 393-400.
In his: Collect. repr., 1882-92, ii, no. 94.

Annual address. The license to practice. J. Am. M. Ass., Chicago, 1889, xii, 649-654.
Also: Maryland M. J., Balt., 1889, xxi, 61-67.
Also: Tr. M. & Chir. Fac. Maryland, Balt., 1889, 70-82.
In his: Collect. repr., 1882-92, ii, no. 96.

Note on intrathoracic growths developing from the thyroid gland. Med. News, Phila., 1889, lv, 257.
In his: Collect. repr., 1882-92, ii, no. 98.

On a case of simple idiopathic muscular atrophy, involving the face and the scapulo-humeral muscles. Am. J. M. Sc., Phila., 1889, n. s., xcvi, 261-265.
In his: Collect. repr., 1882-92, ii, no. 99.

Case of syphiloma of the cord of the cauda equina; death from diffuse central myelitis. J. Nerv. & Ment. Dis., N. Y., 1889, n. s., xiv, 499-507.
In his: Collect. repr., 1882-92, ii, no. 100.

Idiocy and feeble-mindedness in relation to infantile hemiplegia; a report of twenty-two cases at the Pennsylvania Institution for Feeble-Minded Children. Alienist & Neurol., St. Louis, 1889, x, 16-23.

1890

On the value of Laveran's organisms in the diagnosis of malaria. Johns Hopkins Hosp. Bull., Balt., 1889-90, i, ii.
In his: Collect. repr., 1882-92, ii, no. 101.

On fever of hepatic origin, particularly the intermittent pyrexia associated with gallstones. Johns Hopkins Hosp. Rep., Balt., 1890, ii, 3-31.
In his: Collect. repr., 1882-92, ii, no. 102.

Cases of post-febrile insanity. Johns Hopkins Hosp. Rep., Balt., 1890, ii, 46-50.
In his: Collect. repr., 1882-92, ii, no. 103.

Rare forms of cardiac thrombi. Johns Hopkins Hosp. Rep., Balt., 1890, ii, 56-61.
In his: Collect. repr., 1882-92, ii, no. 104.

Note on endocarditis in phthisis. Johns Hopkins Hosp. Rep., Balt., 1890, ii, 62-64.
In his: Collect. repr., 1882-92, ii, no. 105.

Tubercular peritonitis; general considerations; tubercular abdominal tumors; curability. Johns Hopkins Hosp. Rep., Balt., 1890, ii, 67-113.
In his: Collect. repr., 1882-92, ii, no. 106.

Acute nephritis in typhoid fever. Johns Hopkins Hosp. Rep., Balt., 1890, ii, 119-128.
In his: Collect. repr., 1882-92, ii, no. 107.

On the amœba in dysentery and in dysenteric liver abscess. Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 53-54.
In his: Collect. repr., 1882-92, ii, no. 108.

On the form of convulsive tic associated with coprolalia, etc. Med. News, Phila., 1890, lvii, 645-647.
In his: Collect. repr., 1882-92, ii, no. 109.

On the symptoms of chronic obstruction of the common bile-duct by gallstones. Ann. Surg., St. Louis, 1890, xi, 161-185.

Ueber die in Dysenterie und dysenterischem Leberabscess vorhandene Amœba. Centralbl. f. Bacteriol. u. Parasitenkr., Jena., 1890, vii, 736-737.

Multiple thrombi-multiple gangrene. (Proc. Johns Hopkins Hosp. Med. Soc., Oct. 22, 1889.) Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 12.

Fatal hemorrhage into a large bronchocele. (Proc. Johns Hopkins Hosp. Med. Soc., Nov. 18, 1889.) Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 23.

Congenital heart disease. (Proc. Johns Hopkins Hosp. Med. Soc., Dec. 2, 1889.) Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 34.

Filaria sanguinis hominis. (Proc. Johns Hopkins Hosp. Med. Soc., Jan. 6, 1890.) Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 48.

Weir Mitchell. Remarks on the occasion of the presentation to the College of Physicians, Phila., of the portrait of Dr. S. Weir Mitchell, April 22, 1890. Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 64.

Aortic insufficiency. (Proc. Johns Hopkins Hosp. Med. Soc., Oct. 20, 1890.) Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 109.

Hereditary chorea. (Proc. Johns Hopkins Hosp. Med. Soc., Oct. 20, 1890.) Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 110.
In his: Collect. repr., 1882-92, ii, no. 114.

General bronchiectasis of left lung, fetid bronchitis; incision of cavity; death. (Proc. Johns Hopkins Hosp. Med. Soc., Oct. 20, 1890.) Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 109.
In his: Collect. repr., 1882-92, ii, no. 115.

1891

A case of sensory aphasia; word-blindness with hemianopsia. Am. J. M. Sc., Phila., 1891, n. s., cl, 219-224.
In his: Collect. repr., 1882-92, ii, no. 110.

Rudolf Virchow: the man and the student. Boston M. & S. J., 1891, cxv, 425-427.
Also: Johns Hopkins Univ. Circ., Balt., 1891, xi, 17-19.
In his: Collect. repr., 1882-92, ii, no. 111.

Diagnosis of tuberculous broncho-pneumonia in children. Arch. Pediat., Phila., 1891, viii, 825-829.
Also: Tr. Am. Pediat. Soc. (N. Y.), 1892, iii, 25-29.
In his: Collect. repr., 1882-92, no. 112.

Doctor and nurse: remarks to the first class of graduates from the Training School for Nurses at The Johns Hopkins Hospital. Balt., 1891, J. Murphy & Co., 11 p. 4°.
In his: Collect. repr., 1882-92, ii, no. 113.

Obstruction of the superior vena cava. (Proc. Johns Hopkins Hosp. Med. Soc., Jan. 5, 1891.) Johns Hopkins Hosp. Bull., Balt., 1891, ii, 40.
In his: Collect. repr., 1882-92, ii, no. 116.

Case of multiple cysticercii. (Proc. Johns Hopkins Hosp. Med. Soc., Feb. 2, 1891.) Johns Hopkins Hosp. Bull., Balt., 1891, ii, 61.
In his: Collect. repr., 1882-92, ii, no. 117.

Disease of the coronary arteries; fibroid heart. Tr. Path. Soc. Phila. (1887-9), 1891, xiv, 106-108.

Acute phthisis; erosion of a large branch of the pulmonary artery; sudden fatal hemoptysis. Tr. Path. Soc. Phila. (1887-9), 1891, xiv, 169.

The diagnosis of broncho-pneumonia (acute and chronic) from tuberculosis. N. York M. J., 1891, liv, 666.

Report on the Koch treatment in tuberculosis. Johns Hopkins Hosp. Bull., Balt., 1891, ii, 7-14.

Remarks on hysteria with paroxysmal inspiratory spasm. (Proc. Johns Hopkins Hosp. Med. Soc., Nov. 17, 1890.) Johns Hopkins Hosp. Bull., Balt., 1891, ii, 18.

Two cases of pernicious malaria. (Proc. Johns Hopkins Hosp. Med. Soc., Oct. 5, 1891.) Johns Hopkins Hosp. Bull., Balt., 1891, ii, 161-162.

1892

The principles and practice of medicine. Designed for the use of practitioners and students of medicine. New York, 1892, D. Appleton & Co., 1079 p. 8°.

Teacher and student. An address delivered on the occasion of the opening of the new building of the College of Medicine and Surgery of the University of Minnesota. Minneapolis, Oct. 4, 1892, Balt., 1892, J. Murphy & Co., 22 p. 8°.
In his: Collect. repr., 1882-92, ii, no. 123.

Collected reprints. Second series. (January 1, 1882-January 1, 1892.) [Balt., 1892.] 8°.

Remarks on specialism. Boston M. & S. J., 1892, cxvi, 457-459.
Also: Med. News, Phila., 1892, ix, 542-544.
Also: Arch. Pediat., Phila., 1892, ix, 481-483.
In his: Collect. repr., 1882-92, ii, no. 118.

The healing of tuberculosis. Climatologist, Phila., 1892, ii, 149-153.
In his: Collect. repr., 1892-7, iii, no. 119.

On the association of congenital wry-neck, with marked facial asymmetry. Arch. Pediat., N. Y., 1892, ix, 81-85.
In his: Collect. repr., 1882-92, ii, no. 120.

Interstitial processes in the central nervous system. Tr. Cong. Am. Phys. & Surg., 1891, N. Haven, 1892, ii, 144-146.
In his: Collect. repr., 1892-7, iii, no. 121.

The cold-bath treatment of typhoid fever. Med. News, Phila., 1892, lxi, 628-631.
In his: Collect. repr., 1892-7, iii, no. 122.

Notes on the diagnosis and treatment of cholera. Med. News, Phila., 1892, lxi, 290.

License to practice. Northwest Lancet, St. Paul, 1892, xii, 838.

An acute myxedematous condition occurring in goitre. (Proc. Johns Hopkins Hosp. Med. Soc., Dec. 7, 1891.) Johns Hopkins Hosp. Bull., Balt., 1892, iii, 42.

Chronic cerebro-spinal meningitis. (Proc. Johns Hopkins Hosp. Med. Soc., Oct. 17, 1892.) Johns Hopkins Hosp. Bull., Balt., 1892, iii, 119.

Localized pyo-pneumothorax. (Proc. Johns Hopkins Hosp. Med. Soc., Oct. 17, 1892.) Johns Hopkins Hosp. Bull., Balt., 1892, iii, 19.

1893

Note on arsenical neuritis following the use of Fowler's solution. (5451m18.) Montreal M. J., 1892-3, xxi, 721-724.
In his: Collect. repr., 1892-7, iii, no. 130.

Note on a remarkable house epidemic of typhoid fever. Univ. M. Mag., Phila., 1892-3, v, 522-524.
In his: Collect. repr., 1892-7, iii, no. 131.

Tuberculous pericarditis. Am. J. M. Sc., Phila., 1893, n. s., cv, 20-27.
In his: Collect. repr., 1892-7, iii, no. 124.

On dilatation of the colon in young children. Arch. Pediat., N. Y., 1893, x, 111-119.
Also: (Proc. Johns Hopkins Hosp. Med. Soc., Jan. 16, 1893.) Johns Hopkins Hosp. Bull., Balt., 1893, iv, 41-43.
In his: Collect. repr., 1892-7, iii, no. 125.

Physic and physicians as depicted in Plato. Boston M. & S. J., 1893, cxxviii, 129; 153.
In his: Collect. repr., 1892-7, iii, no. 126.

Case of arterio-venous aneurism of the axillary artery and vein of fourteen years' duration. Ann. Surg., Phila., 1893, xvii, 37-40.
In his: Collect. repr., 1892-7, iii, no. 127.

The chronic intermittent fever of endocarditis. Practitioner, Lond., 1893, i, 181-190.
In his: Collect. repr., 1892-7, iii, no. 128.

Remarks on the varieties of chronic chorea, and a report upon two families of the hereditary form, with one autopsy. J. Nerv. & Ment. Dis., N. Y., 1893, xx, 97-111.
In his: Collect. repr., 1892-7, iii, no. 129.

Cases of sub-phrenic abscess. Tr. Ass. Am. Physicians, Phila., 1893, viii, 257-267.
Also: Canad. Fract., Toronto, 1893, xviii, 565-574.
In his: Collect. repr., 1892-7, iii, no. 132.

Shattuck lecture. Mass. Med. Soc., 1893. Tuberculous pleurisy. Boston M. & S. J., 1893, cxxix, 53; 81; 109; 134.
Also: Med. Communicat. Mass. M. Soc., Boston, 1893, xvi, 49-112.
In his: Collect. repr., 1892-7, iii, no. 133.

Profound toxemia with slight tuberculous lesions. Med. News, Phila., 1893, lxxiii, 632.

Jean Martin Charcot, memorial notice. Johns Hopkins Hosp. Bull., Balt., 1893, iv, 87-88.

On sporadic cretinism in America. *Tr. Am. J. Am. Physicians*, Phila., 1893, viii, 380-398.

Also: *Am. J. M. Sc.*, Phila., 1893, n. s., cvi, 503-518.

In his: *Collect. repr.*, 1892-7, iii, no. 136.

Notes on tuberculosis in children. *Arch. Pediat.*, N. Y., 1893, x, 979-986.

In his: *Collect. repr.*, 1892-7, iii, no. 137.

Hirt, Ludwig. The diseases of the nervous system. A text-book for physicians and students. Transl. with permission of the author by August Hoch, assisted by Frank R. Smith, with an introduction by William Osler, N. Y., 1893. D. Appleton & Co., 698 p. 8°.

1894

Lectures on the diagnosis of abdominal tumors, delivered to the post-graduate class, Johns Hopkins University, 1893. New York, 1894, D. Appleton & Co., 192 p. 8°.

Also: *N. York M. J.*, 1894, lix, 129; 161; 193; 260; 385; 417; 481; 545; 577; lx, 65; 97.

In his: *Collect. repr.*, 1892-7, iii, no. 146.

On chorea and choreiform affections. Phila., P. Blakiston, Son & Co., 1894, 125 p. 8°.

In his: *Collect. repr.*, 1892-7, iii, no. 149.

Tuberculosis.

In: *Am. Text-Bk. Dis. Child.* (Starr), Phila., 1894, 94-126.

In his: *Collect. repr.*, 1892-7, iii, no. 134.

Diseases of the blood.

In: *Text-book Theory & Pract. Med.* (Pepper), Phila., 1894, ii, 182-233.

In his: *Collect. repr.*, 1892-7, iii, no. 135.

Diseases of the suprarrenal capsules and ductless glands.

In: *Text-book Theory & Pract. Med.* (Pepper), Phila., 1894, ii, 234-246.

Toxaemia in tuberculosis. *Practitioner*, Lond., 1894, lii, 26-30.

In his: *Collect. repr.*, 1892-7, iii, no. 138.

Parotitis in pneumonia. Case of pericarditis treated by incision and drainage. *Univ. M. Mag.*, Phila., 1893-4, vi, 245-249.

In his: *Collect. repr.*, 1892-7, iii, no. 139.

The army surgeon. An address delivered at the closing exercises of the Army Medical School, Washington, D. C., Feb. 28, 1894. *Med. News*, Phila., 1894, lxi, 318-322.

In his: *Collect. repr.*, 1892-7, iii, no. 147.

The heaven of science. An address delivered at the opening of the Wistar Institute of Anatomy and Biology of the University of Pennsylvania, May 21, 1894. *Univ. M. Mag.*, Phila., 1893-4, vi, 573-586.

In his: *Collect. repr.*, 1892-7, iii, no. 148.

Oliver Wendell Holmes. *Johns Hopkins Hosp. Bull.*, Balt., 1894, v, 85-88.

In his: *Collect. repr.*, 1892-7, iii, no. 150.

The heart in chorea minor. *Med. Chron.*, Manchester, 1894, n. s., i, 321-332.

Clinical remarks on a case of typhoid fever, complicated with bronchitis and laryngitis. *Maryland M. J.*, Balt., 1894, xxxi, 1-3.

The registration of pulmonary tuberculosis. *Phila. Polyclin.*, 1894, iii, 65.

Case of hereditary chorea. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Oct. 1, 1894.) *Johns Hopkins Hosp. Bull.*, Balt., 1894, v, 119-120.

1895

The principles and practice of medicine. Designed for the use of practitioners and students of medicine. 2. ed. New York, 1895, D. Appleton & Co., 1143 p. 8°.

Report on typhoid fever. I. General analysis and summary of the cases. II. Treatment of typhoid fever. III. A study of the fatal cases. IV. Notes on special features, symptoms and complications. *Johns Hopkins Hosp. Rep.*, Balt., 1894-5, iv, 1-72.

In his: *Collect. repr.*, 1892-7, iii, nos. 140-143.

On the neurosis following enteric fever, known as "the typhoid spine." *Johns Hopkins Hosp. Rep.*, 1894-5, iv, 73-82.

Also: *Am. J. M. Sc.*, Phila., 1894, n. s., cvii, 23-30.

In his: *Collect. repr.*, 1892-7, iii, no. 144.

Typhoid fever in Baltimore. *Johns Hopkins Hosp. Rep.*, Balt., 1894-5, iv, 159-167.

In his: *Collect. repr.*, 1892-7, iii, no. 145.

Introductory remarks to course of clinical demonstrations on typhoid fever. *Maryland M. J.*, Balt., 1894-5, xxxii, 79-82.

In his: *Collect. repr.*, 1892-7, iii, no. 151.

Cancer of the stomach with very rapid course. *Univ. M. Mag.*, Phila., 1894-5, vii, 248-252.

In his: *Collect. repr.*, 1892-7, iii, no. 152.

Teaching and thinking; the two functions of a medical school. *Montreal M. J.*, 1894-5, xxiii, 561-572.

In his: *Collect. repr.*, 1892-7, iii, no. 153.

Case of sporadic cretinism (infantile myxedema) treated successfully with thyroid extract. *Arch. Pediat.*, N. Y., 1895, xii, 105-108.

In his: *Collect. repr.*, 1892-7, iii, no. 154.

Diseases, the direct or indirect result of infection. *Text-book Nerv. Dis. Am. Authors* (Dercum), Phila., 1895, 203-226.

In his: *Collect. repr.*, 1892-7, iii, no. 157.

Studies in typhoid fever; Five years' experience with the cold-bath treatment. *Johns Hopkins Hosp. Rep.*, Balt., 1895, v, 321-326.

Also: *Canada M. Rec.*, Montreal, 1895-6, xxiv, 56-60.

Also: *Med. News*, Phila., 1895, lxvii, 393-395.

Also: *Canada Lancet*, Toronto, 1895-6, xxviii, 261-263.

In his: *Collect. repr.*, 1892-7, iii, no. 158.

Studies in typhoid fever: Analysis and summary of the cases; special features, symptoms, and complications; a study of the fatal cases. *Johns Hopkins Hosp. Rep.*, Balt., 1895, v, 281; 283; 459.

In his: *Collect. repr.*, 1892-7, iii, no. 159.

Neuritis during and after typhoid fever. *Johns Hopkins Hosp. Rep.*, Balt., 1895, v, 397-416.

In his: *Collect. repr.*, 1892-7, iii, no. 160.

Chills in typhoid fever. *Johns Hopkins Hosp. Rep.*, Balt., 1895, v, 445-457.

In his: *Collect. repr.*, 1892-7, iii, no. 161.

The practical value of Laveran's discoveries. *Med. News*, Phila., 1895, lxvii, 561-564.

In his: *Collect. repr.*, 1892-7, iii, no. 162.

On the visceral complications of erythema exudativum multiforme. *Am. J. M. Sc.*, Phila., 1895, n. s., cx, 629-646.

Also: *Select. essays and monog.*, Lond., 1897, 321-347. 8°.

In his: *Collect. repr.*, 1892-7, iii, no. 163.

Case of cerebral hemorrhage in a fetus. *Teratologia*, Lond. & Edinb., 1895, ii, 13.

Hyperpyrexia in typhoid fever. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Oct. 7, 1895.) *Johns Hopkins Hosp. Bull.*, Balt., 1895, vi, 143.

Abscess of the liver, perforating the lung. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Oct. 7, 1895.) *Johns Hopkins Hosp. Bull.*, Balt., 1895, vi, 144.

1896

An Alabama student. *Baltimore, Friedenwald Co.*, 1896, 19 p. 12°.

Also: *Johns Hopkins Hosp. Bull.*, Balt., 1896, vii, 6-11.

In his: *Collect. repr.*, 1892-7, iii, no. 166.

Typhoid fever in country districts. *Maryland M. J.*, Balt., 1895-6, xxxiii, 55-62.

In his: *Collect. repr.*, 1892-7, iii, no. 155.

Visible contractile tumor of the pylorus following ulcer of the stomach. *Montreal M. J.*, 1895-6, xxiv, 81-86.

In his: *Collect. repr.*, 1892-7, iii, no. 156.

John Keats, the apothecary poet. *Baltimore, Friedenwald Co.*, 1896, 18 p. 12°.

Also: *Johns Hopkins Hosp. Bull.*, Balt., 1896, vii, 11-16.

In his: *Collect. repr.*, 1892-7, iii, no. 164.

Thomas Dover, M. D. (of Dover's powder), physician and buccaneer. *Baltimore, Friedenwald Co.*, 1896, 18 p. 12°.

Also: *Johns Hopkins Hosp. Bull.*, Balt., 1896, vii, 1-6.

In his: *Collect. repr.*, 1892-7, iii, no. 165.

Addison's disease. *Med. Bull.*, Phila., 1896, xviii, 81-84.

In his: *Collect. repr.*, 1892-7, iii, no. 168.

On the association of enormous heart hypertrophy, chronic proliferative peritonitis and recurring ascites, with adherent pericardium. *Arch. Pediat.*, N. Y., 1896, xlii, 1-10.

In his: Collect. repr., 1892-7, lii, no. 169.

Hemiplegia in typhoid fever. *J. Nerv. & Ment. Dis.*, N. Y., 1896, n. s., xxi, 295-304.

In his: Collect. repr., 1892-7, iii, no. 170.

Diseases of the blood and the ductless glands.

Am. Text-book Applied Therap., Phila., 1896, 902-927.

In his: Collect. repr., 1892-7, iii, no. 171.

The cerebral complications of Raynaud's disease. *Am. J. M. Sc.*, Phila., 1896, n. s., cxii, 522-529.

In his: Collect. repr., 1892-7, iii, no. 172.

Lectures on angina pectoris and allied states. *N. York M. J.*, 1896, lxiv, 177; 249; 281; 346.

In his: Collect. repr., 1892-7, iii, no. 173.

The study of the fevers of the South. *J. Am. M. Sc.*, Chicago, 1896, xxi, 999-1004.

Treatment of fevers. *Maritime M. News*, Halifax, 1896, viii, 183-186.

Association of American Medical Colleges. *Bull. Am. Acad. M.*, Easton, Pa., 1895-6, ii, 508-510.

Chills in typhoid fever. *Univ. M. Mag.*, Phila., 1895-6, viii, 77-85.

Pleuro-peritoneal tuberculosis. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Nov. 4, 1896.) *Johns Hopkins Hosp. Bull.*, Balt., 1896, vii, 79.

Case of Addison's disease; death during treatment with the suprarenal extract. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Oct. 19, 1896.) *Johns Hopkins Hosp. Bull.*, Balt., 1896, vii, 208-209.

Ephemerides, 1895:

I. Introduction.

II. Heberden's nodes.

III. Geographical tongue.

IV. Buccal leucoplacia.

V. Acute gout in the United States.

VI. Calcification of the auricle.

VII. Arthritis deformans in childhood.

VIII. Unusual types of night-terrors; day-terrors.

IX. Tobacco angina.

X. Unusually persistent oxyuria.

XI. Is the coin sound distinctive of pneumothorax?

XII. Head-swaying in children.

Montreal M. J., 1895-6, xxiv, 518; 631; 694; 777; 877; 969.

1897

Lectures on angina pectoris and allied states. *New York*, 1897, D. Appleton & Co., 160 p. 8°.

Collected reprints. Third series. (January 1, 1892-January 1, 1897. [Balt., 1897.]

On six cases of Addison's disease, with the report of a case greatly benefited by the use of the suprarenal extract. *Internat. M. Mag.*, Phila., 1896-7, v, 3-11.

In his: Collect. repr., 1892-7, iii, no. 167.

On the classification of the tics or habit movements. *Arch. Pediat.*, N. Y., 1897, xiv, 1-5.

In his: Collect. repr., 1897-1902, iv, no. 174.

On certain features in the prognosis of pneumonia. *Am. J. M. Sc.*, Phila., 1897, n. s., cxliii, 1-10.

Also: *North Car. M. J.*, Wilmington, 1897, xxxix, 295-307.

In his: Collect. repr., 1897-1902, iv, no. 175.

Mitral stenosis; sudden death; ball thrombus in the left auricle. *Montreal M. J.*, 1896-7, xxv, 729-731.

In his: Collect. repr., 1897-1902, iv, no. 176.

The diagnosis of malarial fever. *Med. News*, N. Y., 1897, lxx, 289-292.

In his: Collect. repr., 1897-1902, iv, no. 177.

On certain unusual forms of paraesthetic meralgia. *J. Nerv. & Ment. Dis.*, N. Y., 1897, xxiv, 131-137.

In his: Collect. repr., 1897-1902, iv, no. 178.

The functions of a state faculty. President's address delivered before the Medical and Chirurgical Faculty of Maryland, at the 99th annual session, Baltimore, Md. April 27, 1897. *Maryland M. J.*, Balt., 1897, xxxvii, 73-77. *Tr. M. & Chir. Fac. Maryland*, Balt., 1897, 21-29.

In his: Collect. repr., 1897-1902, iv, no. 179.

A case of leprosy, with exhibition of patient. *Maryland M. J.*, Balt., 1897, xxxvii, 417-419.

Hemorrhage from the bowels in typhoid fever. *Maryland M. J.*, Balt., 1896-7, xxxvi, 73-75.

Ephemerides, 1897:

XIII. Rheumatic neuritis associated with subcutaneous fibroid nodules.

XIV. Bright's disease or myxedema.

XV. Remarkable noisy expiration in chronic emphysema.

XVI. Chills and fevers in post-partum anemia.

XVII. Lineæ albicantes.

XVIII. Two cases of general bromidrosis.

XIX. Vertigo and ocular defects.

Montreal M. J., 1896-7, xxv, 642; 794; 890; 952.

A clinical lecture on the ball-valve gall-stone in the common duct. *Lancet*, Lond., 1897, i, 1319-1323.

In his: Collect. repr., 1897-1902, iv, no. 180.

Nurse and patient. An address. *Baltimore*, 1897, J. Murphy & Co., 17 p. 8°.

In his: Collect. repr., 1897-1902, iv, no. 181.

Influence of Louis on American medicine. *Johns Hopkins Hosp. Bull.*, Balt., 1897, viii, 161-167.

In his: Collect. repr., 1897-1902, iv, no. 182.

British medicine in Greater Britain. The address in medicine at the British Medical Association, Montreal, meeting. *Boston M. & S. J.*, 1897, cxxxvii, 221-227.

Also: *Med. News*, N. Y., 1897, lxxi, 293-301.

Also: *Med. Rec.*, N. Y., 1897, lii, 333-340.

Also: *Montreal M. J.*, 1897, xxvi, 186-203.

In his: Collect. repr., 1897-1902, iv, no. 183.

Hepatic complications of typhoid fever. *Tr. Ass. Am. Physicians*, Phila., 1897, xii, 378-398.

Also: *Edinb. M. J.*, 1897, n. s. ii, 423-439.

In his: Collect. repr., 1897-1902, iv, no. 184.

Internal medicine as a vocation. *Med. News*, N. Y., 1897, lxxi, 660-663.

In his: Collect. repr., 1897-1902, iv, no. 185.

Pneumonia; a review of the cases studied by the third and fourth classes, Johns Hopkins Hospital, session of 1896-97. *Nat. M. Rev.*, Wash., 1897-8, vii, 177-180.

In his: Collect. repr., 1897-1902, iv, no. 186.

Occasional notes on American medical classics; introductory lecture to a course of clinical observations in the Pennsylvania Hospital, delivered there on the 3d of December, 1776, by Dr. Thomas Bond. *Univ. M. Mag.*, Phila., 1897-8, x, 136-140.

In his: Collect. repr., 1897-1902, iv, no. 187.

Sporadic cretinism in America. *Am. J. M. Sc.*, Phila., 1897, cxiv, 377-401.

Also: *Tr. Cong. Am. Phys. & Surg.*, N. Haven, 1897, iv, 169-206.

In his: Collect. repr., 1897-1902, iv, no. 188.

Address in medicine. *Brit. M. J.*, Lond., 1897, ii, 576-581.

Also [Abstr.]: *Lancet*, Lond., 1897, ii, 584-589.

Also: *Brit. M. Ass. Dally J.*, Montreal, 1897, Part 3, 42-50.

Address in medicine, at the sixty-fifth annual meeting of the British Medical Association, Montreal, Aug. 31 to Sept. 4, 1897. *J. Am. M. Ass.*, Chicago, 1897, xxix, 507-512.

La médecine anglaise dans la Nouvelle Angleterre. [Trans.] *Union méd. du Canada*, Montréal, 1897, xxvi, 595-599.

Relapses in typhoid fever. *J. Am. M. Ass.*, Chicago, 1897, xxix, 97.

The disguises of typhoid fever. *Gaillard's M. J.*, N. Y., 1897, lxiv, 350-352.

Tuberculosis. *Syst. Pract. M.* (Loomis), N. Y. & Phila., 1897, i, 731-848.

1898

The principles and practice of medicine. Designed for the use of practitioners and students of medicine. 3. ed. New York, 1898, D. Appleton & Co., 1181 p. 8°.

Spontaneous pneumothorax. Maryland M. J., Balt., 1897-8, xxxviii, 461-463.

Pneumonia. J. Pract. Med., N. Y., 1897-8, viii, 308-311.

On chronic symmetrical enlargement of the salivary and lachrymal glands. Am. J. M. Sc., Phila., 1898, cxv, 27-30.

In his: Collect. repr., 1897-1902, iv, 189.

On some of the intestinal features of typhoid fever. Phila. M. J., 1898, i, 30-32.

In his: Collect. repr., 1897-1902, iv, no. 190.

Ein Fall von Fistula oesophago-pleuro-thoracica. Arch. f. Verdauungskr., Berl., 1898, iii, 383-386.

In his: Collect. repr., 1897-1902, iv, no. 191.

The relation of typhoid mortality and sewerage. Maryland M. J., Balt., 1897-8, xxxviii, 217-218.

In his: Collect. repr., 1897-1902, iv, no. 192.

Leprosy in the United States, with the report of a case. Johns Hopkins Hosp. Bull., Balt., 1898, ix, 47-49.

In his: Collect. repr., 1897-1902, iv, no. 193.

On diffuse scleroderma; with special reference to diagnosis, and to the use of the thyroid-gland extract. J. Cutan. & Genito-urin. Dis., N. Y., 1898, xvi, 49; 127.

In his: Collect. repr., 1897-1902, iv, no. 194.

Cerebral features of pneumonia. Maryland M. J., Balt., 1897-8, xxxviii, 381-383.

In his: Collect. repr., 1897-1902, iv, no. 195.

Cerebro-spinal fever. Maryland M. J., Balt., 1898, xxxix, 717-723.

In his: Collect. repr., 1897-1902, iv, no. 196.

The arthritis of cerebro-spinal fever. Boston M. & S. J., 1898, cxxxix, 641-643.

In his: Collect. repr., 1897-1902, iv, no. 197.

Ephemerides, 1897:

XX. The blood coagulation time in jaundice.

XXI. Facial paralysis with herpes zoster.

XXII. Paralysis of the ocular muscles in albuminuria.

Montreal M. J., 1898, xxvii, 36-38.

Tuberculosis. Am. Text-Bk. Dis. Child. (Starr), 2. ed. Phila., 1898, 270-302.

1899

On the study of pneumonia. St. Paul M. J., St. Paul, Minn., 1899, i, 5-9.

In his: Collect. repr., 1897-1902, iv, no. 198.

The problem of typhoid fever in the United States. Baltimore, 1899, J. Murphy Co., 13 p. 8°.

Also: Albany M. Ann., 1899, xx, 121-130.

Also: Med. News, N. Y., 1899, lxxiv, 225-229.

In his: Collect. repr., 1897-1902, iv, no. 199.

An acute myxedematous condition with tachycardia, glycosuria, melæna, mania, and death. J. Nerv. & Ment. Dis., N. Y., 1899, xxvi, 65-71.

In his: Collect. repr., 1897-1902, iv, no. 200.

The clinical features of sporadic trichinosis. Am. J. M. Sc., Phila., 1899, n. s., cxvii, 251-265.

In his: Collect. repr., 1897-1902, iv, no. 201.

In memoriam, William Pepper. Phila. M. J., 1899, iii, 607-611.

In his: Collect. repr., 1897-1902, iv, no. 202.

Chronic splenic enlargement with recurring gastro-intestinal hæmorrhages. Edinb. M. J., 1899, n. s., v, 441-453.

In his: Collect. repr., 1897-1902, iv, no. 204.

Cavendish lecture. On the etiology and diagnosis of cerebro-spinal fever. [London, 1899.] 46 p. 8°.

Also: West. Lond. M. J., Lond., 1899, iv, 145-188.

Also: Brit. M. J., Lond., 1899, i, 1517-1529.

Also: Boston M. & S. J., 1899, cxli, 1; 32.

Also: Canad. Pract. & Rev., Toronto, 1899, xxv [xxiv], 447-455.

Also: Lancet, Lond., 1899, i, 1699-1709.

Also: Phila. M. J., 1899, iv, 26-41.

In his: Collect. repr., 1897-1902, iv, no. 205.

After twenty-five years. An address at the opening of the session of the medical faculty, McGill University, Sept. 21, 1899.

Montreal M. J., 1899, xxviii, 823-833.

In his: Collect. repr., 1897-1902, iv, no. 206.

The diagnosis of typhoid fever. A discussion at the New York State Medical Association, October 25, 1899. N. York M. J., 1899, lxx, 673-676.

In his: Collect. repr., 1897-1902, iv, no. 207.

Clinical remarks on hypertrophic cirrhosis of the liver with bronzing of the skin: hæmochromatosis. Brit. M. J., Lond., 1899, ii, 1595-1596.

In his: Collect. repr., 1897-1902, iv, no. 208.

On the medical tests for admission to the public services (Discussion). Brit. M. J., Lond., 1899, ii, 574.

The preventive and remedial treatment of tuberculosis (Discussion). Brit. M. J., Lond., 1899, ii, 1155.

Blood parasites of frogs. N. York M. J., 1899, lxxix, 63.

Clinical microscopy at Johns Hopkins Medical School, Baltimore, United States of America. Brit. M. J., Lond., 1899, i, 69-70.

1900

On splenic anæmia. Am. J. M. Sc., Phila., 1900, n. s., cxix, 54-73.

In his: Collect. repr., 1897-1902, iv, no. 209.

The home treatment of consumption. Maryland M. J., Balt., 1900, xliii, 8-12.

Also: Med. Mirror, St. Louis, 1900, xi, 165-169.

In his: Collect. repr., 1897-1902, iv, no. 210.

A case of multiple gangrene in malarial fever. Johns Hopkins Hosp. Bull., Balt., 1900, xi, 41-42.

In his: Collect. repr., 1897-1902, iv, no. 211.

The visceral lesions of the erythema group. Brit. J. Dermat., Lond., 1900, xii, 227-245.

In his: Collect. repr., 1897-1902, iv, no. 213.

An address on the importance of post-graduate study. Lancet, Lond., 1900, ii, 73-75.

In his: Collect. repr., 1897-1902, iv, no. 214.

Elisha Barlett, a Rhode Island philosopher. An address delivered before the Rhode Island Medical Society, Dec. 7, 1899. With an appendix containing Dr. Barlett's sketch of Hippocrates. Providence, 1900, Snow & Furnham, 43 p. 8°.

Also: Boston M. & S. J., 1900, cxlii, 49; 77.

In his: Collect. repr., 1897-1902, iv, no. 215.

An address on John Locke as a physician. Delivered before the Students' Societies of the Medical Department of the University of Pennsylvania on Jan. 16, 1900. Lancet, Lond., 1900, ii, 1115-1123.

In his: Collect. repr., 1897-1902, iv, no. 216.

Hemiplegia in typhoid fever. Johns Hopkins Hosp. Rep., Balt., 1900, viii, 363-371.

In his: Collect. repr., 1897-1902, iv, no. 217.

Hepatic complications of typhoid fever. Johns Hopkins Hosp. Rep., Balt., 1900, viii, 373-383.

In his: Collect. repr., 1897-1902, iv, no. 218.

Analysis and general summary of the cases [of typhoid fever] from 1889-1899. Johns Hopkins Hosp. Rep., Balt., 1900, viii, 421-422.

In his: Collect. repr., 1897-1902, iv, no. 219.

Special features, symptoms and complications [of typhoid fever]: Johns Hopkins Hosp. Rep., Balt., 1900, viii, 423-486.

In his: Collect. repr., 1897-1902, iv, no. 220.

On the study of tuberculosis. Phila. M. J., 1900, vi, 1029-1030.

In his: Collect. repr., 1897-1902, iv, no. 221.

General summary of the cases of typhoid fever in The Johns Hopkins Hospital for ten years. Phila. M. J., 1900, vi, 696-697.

Fatal angina pectoris without lesions of the coronary arteries in a young man. Med. News, N. Y., 1900, lxxvii, 974-976.

The centenary of the Royal College of Surgeons (Correspondence). Maryland M. J., Balt., 1900, xliiii, 520-522.

Osler, W., & McCrae, T. Cancer of the stomach. A clinical study. Phila., 1900, P. Blakiston's Son & Co., 157 p. 8°.

Osler, W., & McCrae, T. Cancer of the stomach in the young. N. York M. J., 1900, lxxi, 581-585.

Osler, W., & McCrae, T. A study of the blood in cancer of the stomach. N. York M. J., 1900, lxxi, 757-761.

Osler, W., & McCrae, T. Latent cancer of the stomach. Phila. M. J., 1900, v, 245-247.
In his: Collect. repr., 1897-1902, iv, no. 212.

1901

The principles and practice of medicine. Designed for the use of practitioners and students of medicine. 4. ed. New York, 1901, D. Appleton & Co., 1182 p. 8°.

Sporadic cretinism (infantile and juvenile myxœdema).
In: Cycl. Dis. Child., M. & S. (Keating), Phila., 1901, v, 359-371.
In his: Collect. repr., 1897-1902, iv, 203.

Cerebro-spinal fever.

In: Cycl. Dis. Child., M. & S. (Keating), Phila., 1901, v, 1333-1351.

Surgical intervention in perforation in typhoid fever. Phila. M. J., 1901, vii, 138.

On perforation and perforative peritonitis in typhoid fever. Phila. M. J., 1901, vii, 116-119.
Also: St. Louis M. & S. J., 1901, lxxx, 254-264.
In his: Collect. repr., 1897-1902, iv, no. 222.

Books and men. Remarks made at the opening of the new building of the Boston Medical Library, January 12, 1901. Boston M. & S. J., 1901, cxliv, 60-61.
In his: Collect. repr., 1897-1902, iv, no. 223.

The past century; its progress in great subjects. Medicine.

In: Sun, N. Y., 1901, Jan. 27.
In his: Collect. repr., 1897-1902, iv, no. 224.

The progress of medicine in the nineteenth century. [New York, 1901. 8°]
In: Progr. Cent. New York & Lond., 1901, 173-214, 8°.

[“The progress of medicine” the same as “The past century.”]

A plea for the more careful study of the symptoms of perforation in typhoid fever with a view to early operation. Lancet, Lond., 1901, i, 386-387.
In his: Collect. repr., 1897-1902, iv, no. 225.

The medical aspects of carcinoma of the breast, with a note on the spontaneous disappearance of secondary growths. Am. Med., Phila., 1901, i, 17; 63.
In his: Collect. repr., 1897-1902, iv, no. 226.

Hemorrhage in chronic jaundice (Correspondence). Am. Med., Phila., 1901, i, 152.

On the advantages of a trace of albumin and a few tube casts in the urine of certain men above fifty years of age. N. York M. J., 1901, lxxiv, 949-950.
Also: Indian M. Rec., Calcutta, 1902, xxii, 92-93.
In his: Collect. repr., 1897-1902, iv, no. 227.

Congenital absence of the abdominal muscles, with distended and hypertrophied urinary bladder. Johns Hopkins Hosp. Bull., Balt., 1901, xii, 331-333.
In his: Collect. repr., 1897-1902, iv, no. 228.

On a family form of recurring epistaxis, associated with multiple telangiectases of the skin and mucous membranes. Johns Hopkins Hosp. Bull., Balt., 1901, xii, 333-337.
In his: Collect. repr., 1897-1902, iv, no. 229.

The natural method of teaching the subject of medicine. J. Am. M. Ass., Chicago, 1901, xxxvi, 1673-1679.

The study of internal medicine. Med. News, N. Y., 1901, lxxviii, 645-647.

The spinal form of arthritis deformans. Remarks introductory to a discussion on the subject. Tr. Ass. Am. Physicians, Phila., 1901, xvi, 687-689.

1902

The principles and practice of medicine. Designed for the use of practitioners and students of medicine. 5. ed. New York, 1902, D. Appleton & Co., 1079 p. 8°.

Collected reprints. Fourth series. (January 1, 1897-January 1, 1902. [Balt., 1902.]

On the diagnosis of bilateral cystic kidney. Am. Med., Phila., 1902, iii, 463-464.
In his: Collect. repr., 1902-1907, v, no. 230.

On amebic abscess of the liver. Med. News, N. Y., 1902, lxxx, 673-677.
In his: Collect. repr., 1902-1907, v, no. 231.

Amebic dysentery. Therap. Gaz., Detroit, 1902, 3, s. xviii, 217-218.
Also: Proc. Phila. Co. M. Soc., Phila., 1902, n. s., iv, 44-46.
In his: Collect. repr., 1902-1907, v, no. 232.

Note on the occurrence of ascites in solid abdominal tumors. Phila. M. J., 1902, ix, 928-929.
In his: Collect. repr., 1902-1907, v, no. 233.

Alfred Stillé. Univ. Penn. Med. Bull., Phila., 1902, xv, 126-132.
In his: Collect. repr., 1902-1907, v, no. 234.

Notes on aneurism. J. Am. M. Ass., Chicago, 1902, xxxviii, 1483-1486.
In his: Collect. repr., 1902-1907, v, no. 235.

On heredity in bilateral cystic kidney. Am. Med., Phila., 1902, iii, 951.
In his: Collect. repr., 1902-1907, v, no. 236.

Some aspects of American medical bibliography. Address at the meeting of the Association of Medical Librarians, Saratoga, June 10, 1902. Bull. Ass. M. Librar., Balt., 1902, i, 19-32.
Also: Am. Med., Phila., 1902, iv, 424-427.
In his: Collect. repr., 1902-1907, v, no. 237.

Chauvinism in medicine. An address before the Canadian Medical Association, Montreal, Sept. 17, 1902. Phila. M. J., 1902, x, 432-439.
In his: Collect. repr., 1902-1907, v, no. 238.

On splenic anemia. [Second paper.] Am. J. M. Sc., Phila., 1902, cxxiv, 751-770.
Also: Tr. Ass. Am. Physicians, Phila., 1902, xvii, 429-456.
In his: Collect. repr., 1902-1907, v, no. 239.

William Beaumont. A pioneer American physiologist. An address before the St. Louis Medical Society, Oct. 4, 1902. St. Louis, 1902, 29 p. 8°.
Also: J. Am. M. Ass., Chicago, 1902, xxxix, 1223-1231.
In his: Collect. repr., 1902-1907, v, no. 240.

A note on the treating of the history of medicine. Brit. M. J., Lond., 1902, ii, 93.

Intermittent claudication. Montreal M. J., 1902, xxxi, 81-86.

A visit to the Hunterian Library at Glasgow. Bull. Ass. M. Librar., Balt., 1902, i, 20-23.

1903

Case of leukæmia. Virginia M. Semi-Month., Richmond, 1902-3, vii, 540.

On the need of a radical reform in our methods of teaching senior students. Med. News, N. Y., 1903, lxxxii, 49-53.
In his: Collect. repr., 1902-1907, v, no. 241.

Aneurism of the descending thoracic aorta. Phila., 1903, J. B. Lippincott Co., 40 p. 8°.
Also: Internat. Clin., Phila., 1903, 13, s. i, 1-40.
In his: Collect. repr., 1902-1907, v, no. 242.

On the educational value of the medical society. Boston M. & S. J., 1903, cxlviii, 275-279.
In his: Collect. repr., 1902-1907, v, no. 243.

A case of chronic purpuric erythema (eight years' duration) with pigmentation of skin and enlargement of liver and spleen. J. Cutan. Dis. incl. Syph., N. Y., 1903, xxi, 297-302.
In his: Collect. repr., 1902-1907, v, no. 244.

On obliteration of the superior vena cava. Johns Hopkins Hosp. Bull., Balt., 1903, xiv, 169-175.
In his: Collect. repr., 1902-1907, v, no. 245.

On the so-called Stokes-Adams disease (slow pulse with syncopal attacks, etc.). Lancet, Lond., 1903, ii, 516-524.
In his: Collect. repr., 1902-1907, v, no. 246.

Chronic cyanosis with polycythemia and enlarged spleen; a new clinical entity. Am. J. M. Sc., Phila., 1903, n. s., cxxvi, 187-201.
Also: Tr. Ass. Am. Physicians, Phila., 1903, xviii, 299-325.
In his: Collect. repr., 1902-1907, v, no. 247.

The master-word in medicine. An address to medical students on the occasion of the opening of the new buildings of the Medical Faculty of the University of Toronto, Oct. 1, 1903. Baltimore, 1903, J. Murphy & Co., 3 p. 8°.
Also: Brit. M. J., Lond., 1903, ii, 1196-1200.
Also: Canad. J. M. & S., Toronto, 1903, xiv, 333-347.
Also: Montreal M. J., 1903, xxxii, 771-785.
Also: Johns Hopkins Hosp. Bull., Balt., 1904, xv, 1-7.
In his: Collect. repr., 1902-1907, v, no. 248.

Typhoid fever and tuberculosis. *Am. Med., Phila.*, 1903, vi, 1015-1016.
In his: Collect. repr., 1902-1907, v, no. 249.

The home in its relation to the tuberculosis problem. *Med. News, N. Y.*, 1903, lxxxiii, 1105-1110.
In his: Collect. repr., 1902-1907, v, no. 250.

On the visceral manifestations of the erythema group of skin diseases. *Tr. Ass. Am. Physicians, Phila.*, 1903, xviii, 599-624.
Also: *Am. J. M. Sc., Phila.*, 1904, cxxvii, 1-23.
In his: Collect. repr., 1902-1907, v, no. 251.

Diabetes in infancy. *Phila. M. J.*, 1903, xi, 538.

The significance of cutaneous angiomas. *Med. News, N. Y.*, 1903, lxxxiii, 91.

The varieties of lineæ albicantes. *Med. News, N. Y.*, 1903, lxxxiii, 904.

Aneurism of upper part of thoracic aorta. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Oct. 20, 1902.) *Johns Hopkins Hosp. Bull., Balt.*, 1903, xiv, 85.

Certain forms of cyanosis with polycythæmia. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Nov. 17, 1902.) *Johns Hopkins Hosp. Bull.*, 1903, xiv, 91.
Also: Maryland M. J., Balt., 1903, xvi, 81-82.

Two cases of cirrhosis of the liver in children. (*Proc. Johns Hopkins Hosp. Med. Soc.*, March 16, 1903.) *Johns Hopkins Hosp. Bull., Balt.*, 1903, xiv, 322.

1904

Aequanimitas, with other addresses to medical students, nurses and practitioners of medicine. *Phila.*, 1904, P. Blakiston's Son & Co. 389 p. 12°.

The same. *Lond.*, 1904, H. K. Lewis, 389 p. 12°.

The Ingersoll lecture, 1904. Science and immortality. Boston, 1904, Houghton, Mifflin & Co. 60 p. 12°.

The "phthisiologia" of Richard Morton, M.D. *Med. Libr. & Hist. J., Brooklyn*, 1904, ii, 1-7.
In his: Collect. repr., 1902-1907, v, no. 252.

Ochronosis: the pigmentation of cartilages, sclerotics, and skin in alkaptonuria. *Lancet, Lond.*, 1904, i, 10-11.
In his: Collect. repr., 1902-1907, v, no. 253.

On the surgical importance of the visceral crises in the erythema group of skin diseases. *Am. J. M. Sc., Phila. & N. Y.*, 1904, n. s., cxxvii, 751-754.
Also: *Johns Hopkins Hosp. Bull., Balt.*, 1904, xv, 259-261.
In his: Collect. repr., 1902-1907, v, no. 254.

Angina pectoris and arterio-sclerosis. *J. Am. M. Ass., Chicago*, 1904, xliii, 775.

Chronic cyanotic polycythæmia with enlarged spleen. *Brit. M. J., Lond.*, 1904, i, 121.

Korsakoff's disease. *N. York M. J. [etc.]*, 1904, lxxix, 570.

Vasomotor mottling. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Nov. 16, 1903.) *Johns Hopkins Hosp. Bull., Balt.*, 1904, xv, 66.

Aneurism of arch of aorta and innominate. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Nov. 16, 1903.) *Johns Hopkins Hosp. Bull., Balt.*, 1904, xv, 66.

Remarks at the unveiling of the memorial tablet to Dr. Jesse W. Lazear. *Johns Hopkins Hosp. Bull., Balt.*, 1904, xv, 387-388.

The home in its relation to the tuberculosis problem. *Sanitarian, N. Y.*, 1904, lii, 322-336.
Also: *Canada Lancet, Toronto*, 1904-5, xxxviii, 600-612.

1905

The principles and practice of medicine, designed for the use of practitioners and students of medicine. 6. ed. *N. Y. & Lond.*, 1905, D. Appleton & Co. 1143 p. 8°.

Counsels and ideals from the writings of . . . [Selected and edited by C. N. B. Camac.] *Bost. & N. Y.*, 1905, Houghton, Mifflin & Co. 277 p. 12°.

Unity, peace, and concord: a farewell address to the medical profession of the United States. *Oxford*, 1905, H. Hart, 22 p. 8°.
Also: *J. Am. M. Ass., Chicago*, 1905, xlv, 365-369.
Also: *St. Louis M. Rev.*, 1905, lii, 112-116.
Also: Maryland M. J., Balt., 1905, xlviii, 412-422.
In his: Collect. repr., 1902-1907, v, no. 255.

The student life. A farewell address to Canadian and American medical students. *Oxford* [1905.] H. Hart. 32 p. 8°.

Also: *Canada Lancet, Toronto*, 1905-6, xxxix, 121-138.

Also: *Med. News, N. Y.*, 1905, lxxxvii, 625-633.

Also: *St. Louis M. Rev.*, 1905, lii, 273-283.

In his: Collect. repr., 1902-1907, v, no. 256.

Aneurism of the abdominal aorta. *Lancet, Lond.*, 1905, ii, 1089-1096.

In his: Collect. repr., 1902-1907, v, no. 257.

Acute tuberculous pneumonia. *Brooklyn M. J.*, 1905, xix, 57-61.

The home in its relation to the tuberculosis problem. *Rev. internat. de la tuberc.*, Par., 1905, vii, 403-413.

Also: *Rep. Henry Phipps Inst. study . . . tuberculosis, Phila.*, 1905, i, 141-154.

Also: *Am. J. Tuberc., Detroit*, 1905, i, 9-15.

An address on Sir Thomas Browne. *Brit. M. J., Lond.*, 1905, ii, 993-998.

The Royal Dental Hospital of London: address. *Lancet, Lond.*, 1905, ii, 1210.

Valedictory address at Johns Hopkins University. *J. Am. M. Ass., Chicago*, 1905, xlv, 705-710.

Biliary cirrhosis of family type. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Nov. 7, 1904.) *Johns Hopkins Hosp. Bull., Balt.*, 1905, xvi, 112-113.

Report of a case of ulcerative endocarditis, with embolism of the aorta. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Dec. 19, 1904.) *Johns Hopkins Hosp. Bull., Balt.*, 1905, xvi, 118.

Report of a case of arterio-venous aneurism of the thigh. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Dec. 19, 1904.) *Johns Hopkins Hosp. Bull., Balt.*, 1905, xvi, 119.

A case of arterio-venous aneurism. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Jan. 16, 1905.) *Johns Hopkins Hosp. Bull., Balt.*, 1905, xvi, 146.

Résumé of history of blood platelets. (*Proc. Johns Hopkins Hosp. Med. Soc.*, March 6, 1905.) *Johns Hopkins Hosp. Bull., Balt.*, 1905, xvi, 200.

A letter to graduates of The Johns Hopkins Medical School. *Johns Hopkins Hosp. Bull., Balt.*, 1905, xvi, 410.

1906

Aequanimitas, with other addresses to medical students, nurses, and practitioners of medicine. 2. ed. with three additional addresses. *Phila.*, 1906, P. Blakiston's Son & Co. 475 p. 8°.

The same, *Lond.*, 1906, H. K. Lewis, 485 p. 8°.

Convulsions in typhoid fever. *Practitioner, Lond.*, 1906, lxxvi, 1-8.

In his: Collect. repr., 1902-1907, v, no. 258.

On the medical aspects of carcinoma of the breast. *Brit. M. J., Lond.*, 1906, i, 1-4.

In his: Collect. repr., 1902-1907, v, no. 259.

Angina pectoris as an early symptom in aneurism of the aorta. *Med. Chron., Manchester*, 1906, xlv, 69-79.

In his: Collect. repr., 1902-1907, v, no. 260.

Religio medici. An address delivered at Guy's Hospital, October, 1905, *Lond.*, 1906, Chiswick Press, 31 p. 8°.

Also: *Library, Lond.*, 1906, vii, 1-31.

In his: Collect. repr., 1902-1907, v, no. 261.

The growth of truth as illustrated in the discovery of the circulation of the blood. Being the Harveian oration delivered at the Royal College of Physicians, London, October 18, 1906. *Lond.*, 1906, H. Frowde. 44 p. 8°.

Also: *Brit. M. J., Lond.*, 1906, ii, 1077-1084.

Also: *Lancet, Lond.*, 1906, ii, 1113-1120.

Also: *Boston M. & S. J.*, 1906, civ, 491-502.

In his: Collect. repr., 1902-1907, v, no. 262.

Fracastorius. *Proc. Charaka Club, N. Y.*, 1906, ii, 5-20.

In his: Collect. repr., 1902-1907, v, no. 263.

Address of the Vice-President. *Nat. Ass. Study & Prevent. Tuberculosis, Trans., N. Y.*, 1906, i, 20-27.

John Radcliffe [the first possessor of the "gold-headed cane."] *Johns Hopkins Hosp. Bull., Balt.*, 1906, xvii, 163-165.

1907

- Collected reprints. Fifth series. (January 1, 1902-January 1, 1907.) [Balt., 1907.]
- The Royal Medical Society of Edinburgh: particularly its relations with the profession of the United States and Canada. Scot. M. & S. J., Edinb., 1907, xx, 239-246.
- Cerebrospinal fever. Edinb. M. J., 1907, n. s., xxi, 199-204.
- The early diagnosis of cancer of the stomach. Brit. M. J., Lond., 1907, i, 746.
- On the library of a medical school. Johns Hopkins Hosp. Bull., Balt., 1907, xviii, 109-111.
- On telangiectasis circumscripta universalis. Johns Hopkins Hosp. Bull., Balt., 1907, xviii, 401-403.
- A clinical lecture on abdominal tumors associated with disease of the testicle. Lancet, Lond., 1907, i, 1409-1412.
- Note on the use of a medical journal. West. Canada M. J., Winnipeg, 1907, i, 1-3.
- The reserves of life. St. Mary's Hosp. Gaz., Lond., 1907, xiii, 95-98.
- The evolution of internal medicine.
In: Mod. Med. (Osler), Phila. & N. Y., 1907, i, p. xv-xxxiv.
- Osler, W., & Churchman, J. W. Syphilis.
In: Mod. Med. (Osler), Phila. & N. Y., 1907, iii, 436-521.
- Osler, W., & McCrae, T., eds. Modern medicine, its theory and practice. In original contributions by American and foreign authors. v. 1-3, Phila. & N. Y., 1907, Lea Brothers & Co., 8°.
- Osler, W. [et al.]. Discussion on the diagnosis of acute pancreatitis. [Abstr.] Brit. M. J., Lond., 1907, ii, 1132-1135.
- Krehl, Rudolf. Principles of clinical pathology. A text-book for students and physicians. Authorized transl. from the 4. German ed. by Walter Hewlett, with an introduction by William Osler. 2. ed. Phila. & Lond. 1907. J. B. Lippincott Co. 520 p. 8°.
- Quarterly (The) Journal of Medicine. Edited by William Osler [et al.]. Oxford, 1907, v. 1. roy. 8°.

1908

- Thomas Linacre. Cambridge, 1908, University Press, 64 p. 11 pl. 12°.
- An Alabama student, and other biographical essays. N. Y., 1908, Oxford Univ. Press, Am. Branch. 334 p. 8°.
- La pratique de la médecine. Traduction française sur la 6^e édition par M. Solomon et Louis Lazard. Préface du Dr. Pierre Marie. Par., 1908, G. Steinhil. 1230 p. 8°.
- On multiple hereditary telangiectasis with recurring hæmorrhages. Quart. J. Med., Oxford, 1907-8, i, 53-58.
- Splenic polycythæmia with cyanosis. Proc. Roy. Soc. Med., Lond., 1907-8, i, Clin. Sect., 41-43.
- A clinical lecture on erythema (polycythæmia with cyanosis, maladie de Vaquez). Lancet, Lond., 1908, i, 143-146.
- Note on French and German for medical students. Lancet, Lond., 1908, ii, 957.
- Splenic enlargements other than leukæmic. Brit. M. J., Lond., 1908, ii, 1151-1154.
- Remarks on the functions of an out-patient department. Brit. M. J., Lond., 1908, i, 1470-1473.
Also: St. Louis M. Rev., 1908, lviii, 344-346.
- Chronic infectious endocarditis. Quart. J. Med., Oxford, 1908-9, ii, 219-230.
Also: Tribune med., N. Y., 1909, i, v. 29.
- Endocardites infectieuses chroniques. Bull. et mém. Soc. méd. d. hôp. de Par., 1908, 3. s., xxv, 794-796.
Also: Tribune méd., Par., 1908, n. s., xl, 773.
- The pneumococcus infections. Clin. J., Lond., 1907-8, xxxi, 295-301.
Also: Tr. M. Soc., Lond., 1909, xxxi, 93-116.
- Historical note on hereditary chorea. Neurographs, Brooklyn, 1908, i, 113-116.
- Vienna after thirty-four years. J. Am. M. Ass., Chicago, 1908, i, 1523-1525.

Acute endocarditis.

- In: Mod. Med. (Osler), Phila. & N. Y., 1908, iv, 133-150.
- Diseases of the arteries.
In: Mod. Med. (Osler), Phila. & N. Y., 1908, iv, 426-447.
- Aneurysm.
In: Mod. Med. (Osler), Phila. & N. Y., 1908, iv, 448-502.
- Osler, W., & Gibson, A. G. Diseases of the valves of the heart.
In: Mod. Med. (Osler), Phila. & N. Y., 1908, iv, 205-269.
- Osler, W., & McCrae, T., eds. Modern medicine, its theory and practice. In original contributions by American and foreign authors. v. 4-5, Phila. & N. Y., 1908. Lea & Febiger. 8°.

1909

- The principles and practice of medicine, designed for the use of practitioners and students of medicine. 7. ed., N. Y. & Lond., 1909, D. Appleton & Co., 1143 p., 8°.
- Lehrbuch der internen Medizin. Aus dem Englischen übersetzt und für deutsche Verhältnisse ergänzt und bearbeitet, von Priv.-Doz. Dr. Edmund Hoke, mit einem Vorwort von ober-santitätsrat und Hofrat Prof. Dr. R. v. Jaksch. Berlin & Wien, 1909. Urban & Schwarzenberg, 879 p., 8°.
- De la paralysie du nerf récurrent gauche dans les affections mitrales. Arch. d. mal. du cœur [etc.], Par., 1909, ii, 73-76.
- Paralysis of the left recurrent laryngeal nerve in mitral-valve disease. Montreal M. J., 1909, xxxviii, 79-83.
- Remarks on the medical library in post-graduate work. Brit. M. J., Lond., 1909, ii, 925-928.
- Schorstein lecture on syphilis and aneurysm. Brit. M. J., Lond., 1909, ii, 1509-1514.
- The treatment of disease. Lond., 1909, H. Frowde, 26 p., 8°.
Also: Brit. M. J., Lond., 1909, ii, 185-189.
Also: Canad. Lancet, Toronto, 1908-9, xliii, 896-912.
- Note on the relation of the capillary blood-vessels in purpura. Lancet, Lond., 1909, i, 1385.
- An address on the nation and the tropics. Delivered at the London School of Tropical Medicine on Oct. 26, 1909. Lancet, Lond., 1909, ii, 1401-1406.
- Impressions of Paris. J. Am. M. Ass., Chicago, 1909, lli, 701; 771.
- Old and new. Annual oration on the occasion of the opening of the new building of the Medical and Chirurgical Faculty of Maryland, May 13, 1909. J. Am. M. Ass., Chicago, 1909, llii, 4-8.
- Aneurysm.
In: Syst. Med. (Allbutt & Rolleston), Lond., 1909, vi, 620-681.
- Raynaud's disease.
In: Mod. Med. (Osler), Phila. & N. Y., 1909, vi, 625-647.
- Angioneurotic edema; Quincke's disease.
In: Mod. Med. (Osler), Phila. & N. Y., 1909, vi, 648-664.
- Diffuse scleroderma; erythromelalgia.
In: Mod. Med. (Osler), Phila. & N. Y., 1909, vi, 665-682.
- Osler, W., & Keith, A. Stokes-Adams disease.
In: Syst. Med. (Allbutt & Rolleston), Lond., 1909, vi, 130-156.
- Osler, W., & McCrae, T., eds. Modern medicine, its theory and practice. In original contributions by American and foreign authors. v. 6, Phila. & N. Y., 1909, Lea & Febiger, 799 p., 8°.

1910

- The principles and practice of medicine, transl. by Philip B. Cousland. 7. ed. [Chinese text.] Shanghai, 1910, Presby. Mis. Press. 8°.
- In memoriam. Dr. John Hewetson, 1867-1910. Johns Hopkins Hosp. Bull., Balt., 1910, xxi, 357.
- Michael Servetus. Johns Hopkins Hosp. Bull., Balt., 1910, xxi, 1-11.
Also transl.: Deutsche Rev., Stuttg. u. Leipz., 1909, iv, 328-347.
- Certain vasomotor, sensory, and muscular phenomena associated with cervical rib. Am. J. M. Sc., Phila. & N. Y., 1910, cxxxix, 463-472.
- The Lumleian lectures on angina pectoris. Lancet, Lond., 1910, i, 697; 839; 973.
- Female hæmophilias and de novo cases of hæmophilia. Lancet, Lond., 1910, i, 1226.

The faith that heals. Brit. M. J., Lond., 1910, ii, 1470-1472.

The pupil symptoms in thoracic aneurysm: a clinical lecture: Radcliffe Infirmary. Practitioner, Lond., 1910, lxxxiv, 417-422.

Ueber angina pectoris. Allg. Wien. med. Ztg., 1910, iv, 435.

Osler, W., & McCrae, T., eds. Modern medicine, its theory and practice. In original contributions by American and foreign authors. v. 7, Phila. & N. Y., 1910, Lea & Febiger, 969 p., 8°.

1911

Man's redemption of man. Am. Mag., N. Y., 1910-11, lxxi, 246-252.

Transient attacks of aphasia and paralyses in states of high blood pressure and arteriosclerosis. Canad. M. Ass. J., Toronto, 1911, i, 919-926.

An address on the hospital unit in university work. Lancet, Lond., 1911, i, 211-213.

Also: Northumberland & Durham M. J., Newcastle-upon-Tyne, 1910, xviii, 178-189.

Remarks on organization in the profession. Brit. M. J., Lond., 1911, i, 237-239.

Treatment; introductory address. Nat. Ass. Prev. Consumpt. Tr., Lond., 1911, 119-123.

The pathological institute of a general hospital. Glasgow M. J., 1911, lxxvi, 321-333.

Sir Astley Cooper's case of ligature of the abdominal aorta. Guy's Hosp. Gaz., Lond., 1911, xxv, 277.

Sulle telangiectasie emorragiche ereditarie. Riforma med., Napoli, 1911, xxvii, 57-58.

Vallery-Radot, René, The life of Pasteur. Transl. from the French by Mrs. R. D. Devonshire; with a foreword by Sir William Osler, 2 v. Lond., 1911, Constable & Co. 242 p., port; 271 p., 8°.

1912

The principles and practice of medicine. 8. ed., rev. with the assistance of Thomas McCrae. N. Y. & Lond., 1912. D. Appleton & Co., 1250 p., 8°.

A Drake monument. Lancet-Clinic, Cincin., 1912, cvii, 421.

Dr. Robert Fletcher. Bristol M.-Chir. J., 1912, xxx, 289-294, port.

High blood pressure. Its associations, advantages and disadvantages. Brit. M. J., Lond., 1912, ii, 1173-1177.

Chronic infectious endocarditis, with an early history like splenic anemia. Interstate M. J., St. Louis, 1912, xix, 103-107.

Men and books:

I. Nicolaus Steno. Canad. M. Ass. J., Toronto, 1912, ii, 67-68.

II. Les collections artistiques de la Faculté de Médecine de Paris. *Ibid.*, 68-69.

III. Samuel Wilkes. *Ibid.*, 70-71.

IV. Jean Astruc and the higher criticism. *Ibid.*, 151-152.

V. Two Frenchmen on laughter. *Ibid.*, 152-155.

VI. An incident in the life of Harvey. *Ibid.*, 246-247.

VII. Letters of Laennec. *Ibid.*, 247-248.

VIII. Dr. Payne's library. *Ibid.*, 248-249.

IX. The funeral of Lord Lister. *Ibid.*, 343-344.

X. Gui Patin. *Ibid.*, 429-430.

XI. George Bodington. *Ibid.*, 526-527.

XII. Histoire de la Charité. *Ibid.*, 527-528.

XIII. The school of Physic, Dublin. *Ibid.*, 833-835.

XIV. Kelly's American Medical Biography. *Ibid.*, 938-939.

XV. The works of John Caius. *Ibid.*, 1034-1036.

XVI. William Beaumont. *Ibid.*, 1136-1138.

Meyer, Jesse S., Life and letters of Dr. William Beaumont, including hitherto unpublished data concerning the case of Alexis St. Martin. With an introduction by Sir William Osler. St. Louis, 1912. C. V. Mosby Co., 342 p. port. roy., 8°.

1913

Man's redemption of man. A lay sermon, McEwan Hall, Edinburgh, Sunday, July 2, 1910. N. York, 1913. P. B. Hæber, 63 p., 24°.

A way of life. 2. impression. Lond., 1913, Constable & Co., 62 p., 16°.

Address on examinations, examiners and examinees. Brit. M. J., Lond., 1913, ii, 946-948.

Also: Lancet, Lond., 1913, ii, 1047-1050.

Also: Dublin J. M. Sc., 1913, cxxxvi, 313-327.

An arterio-venous aneurysm of the axillary vessels of 30 years' duration. Lancet, Lond., 1913, ii, 1248.

Specialism in the general hospital. Johns Hopkins Hosp. Bull., Balt., 1913, xxiv, 167-171.

Also: Johns Hopkins Alumni Mag., Balt., 1913, i, 275-286.

Case illustrating circulatory disturbance with cervical rib. Proc. Roy. Soc. Med., Lond., 1912-13, vi, Clin. Sect. 9-12.

[Introductory remarks on history of medicine.] Med. Mag., Lond., 1913, xxii, 35.

A down survey manuscript of William Petty. Med. Mag., Lond., 1913, xxii, 36-39.

Also: Proc. Roy. Soc. Med., Lond., 1912-13, vi, Sect. Hist. Med., 2-5.

Presidential address, British Hospitals Association. Med. Mag., Lond., 1913, xxii, 368-372.

Men and books:

XVII. The young Laennec. Canad. M. Ass. J., Toronto, 1913, iii, 137-140.

XVIII. Mediæval Medicine. *Ibid.*, 140-141.

XIX. Robert Fletcher. *Ibid.*, 227-228.

XX. Jacques Benigne Winslow. *Ibid.*, 319-321.

XXI. Aristotle, Greek Thinkers by Gemperz, vol. iv. *Ibid.*, 416-417.

XXII. Dr. Slop. *Ibid.*, 612-613.

XXIII. John Shaw Billings. *Ibid.*, 613-616.

Osler, Sir W., & McCrae, T., eds. Modern medicine: its theory and practice. In original contributions by American and foreign authors. 2. ed. v. 1. Phila. & N. Y., 1913, Lea & Febiger, 1122 p., 8°.

Osler, Sir W., Welch, W. H., [et al.] Memorial meeting in honor of John Shaw Billings. Bull. N. Y., Public Library, 1913, xvii, 511-535.

Also: [Abstr.] Library J., N. Y., 1913, xxxviii, 334-338.

1914

Bacilli and bullets. N. Y., 1914, Oxford Univ., 8 p., 12°.

A way of life. An address to Yale students Sunday evening, April 20, 1913. N. York, 1914. P. B. Hæber, 62 p., 24°.

Syphilis of the liver with the picture of Banti's disease. Proc. Roy. Soc. Med., Lond., 1913-14, vii, Med. Sect., 1-7.

Splenomegaly; two attacks of hæmatemesis; irregular liver. Proc. Roy. Soc. Med., Lond., 1913-14, vii, Clin. Sect., 108.

Suggested scheme for the restoration of the tomb of Avicenna. Proc. Roy. Soc. Med., Lond., 1913-14, vii, Sect. Hist. Med., 280.

Medical notes on England at war. J. Am. M. Ass., Chicago, 1914, lxiii, 2303-2305.

The proposed general catalogue of incunabula. Bull. Med. Library Ass., Balt., 1914, iii, 45-48.

Men and books:

XXIV. Israel and medicine. Canad. M. Ass. J., Toronto, 1914, iv, 729-733.

XXV. "Looking back." 1889. *Ibid.*, 1012-1014.

XXVI. Nathan Smith. *Ibid.*, 1109-1111.

An address on the medical clinic: a retrospect and a forecast. Brit. M. J., Lond., 1914, i, 10-16.

- Early printed medical books. *Brit. M. J.*, Lond., 1914, i, 205.
Also: Lancet, Lond., 1914, i, 255.
- The visceral lesions of purpura and allied conditions. *Brit. M. J.*, Lond., 1914, i, 517-525.
- Some MSS. and books in the Bodleian Library illustrating the evolution of British surgery. *Brit. M. J.*, Lond., 1914, i, 825-826.
- An address at the new pathological laboratory at the Royal Mineral Water Hospital, Bath. *Brit. M. J.*, Lond., 1914, i, 1314-1315.
Also: Lancet, Lond., 1914, i, 1689-1690.
- Bacilli and bullets; an address to the officers and men in the camps at Churn. *Brit. M. J.*, Lond., 1914, ii, 569-570.
Also: Med. Mag., Lond., 1914, xxiii, 580-583.
- Sir James Y. Simpson and anæsthesia (Correspondence). *Lancet*, Lond., 1914, ii, 1067.
- Long and anæsthesia (Correspondence). *Lancet*, Lond., 1914, ii, 1219-1220.
- Syphilis of the liver with the picture of Banti's disease. *Clin. J.*, Lond., 1914, xliii, 462-464.
- Appreciation of Silas Weir Mitchell. *Brit. M. J.*, Lond., 1914, i, 120-121.
- The war and typhoid fever. *Brit. M. J.*, Lond., 1914, ii, 909-913.
Also: Tr. Soc. Trop. M. & Hyg., Lond., 1914-15, viii, 45-74.
- Osler, Sir W., & Churchman, J. W., Syphilis.
In: Mod. Med., 2. ed. (Osler & McCrae), Phila. & N. Y., 1914, ii, 144-215.
- Osler, Sir W., & McCrae, T., eds., Modern medicine, its theory and practice. In original contributions by American and foreign authors. 2. ed., v. 2-3, Phila. & N. Y., 1914, Lea & Febiger, 8°.
- 1915
- Science and war. Oxford, 1915, Clarendon Press, 40 p., 8°.
- Special discussion on the epidemiology of cerebrospinal meningitis. *Proc. Roy. Soc. Med.*, Lond., 1914-15, viii, Epidemiol. & State Med., 41-45.
- The Jonathan Hutchinson iconography. A preliminary note. *Johns Hopkins Hosp. Bull.*, Balt., 1915, xxvi, 82.
- A tribute to Dr. Edward L. Trudeau; a medical pioneer. *Am. Med.*, Burlington, Vt. & N. Y., 1915, n. s., x, 20.
- Remarks on the diagnosis of polycystic kidney. *Internat. Clin.*, Phila., 1915, 25. s., i, 1-5.
- The coming of age of internal medicine in America. *Internat. Clin.*, Phila., 1915, 25. s., iv, 1-5.
- Remarks on arterio-venous aneurysm. *Lancet*, Lond., 1915, i, 949-955.
- Note on acute infectious jaundice. *Lancet*, Lond., 1915, ii, 605.
- An address on science and war. Delivered at the University of Leeds Medical School on October 1, 1915. *Lancet*, Lond., 1915, ii, 795-801.
- Cold-bite + muscle-inertia = trench-foot. *Lancet*, Lond., 1915, ii, 1368.
- Medical notes on England at war. *J. Am. M. Ass.*, Chicago, 1915, lxiv, 679-680; 1512-1513; 2001-2002.
Also: West Canada M. J., Winnipeg, 1915, ix, 59-65.
Also: Dominion M. Month., 1915, xlii, 41; 125.
- Remarks on cerebrospinal fever in camps and barracks. *Brit. M. J.*, Lond., 1915, i, 189.
- Discussion on the treatment of cerebrospinal meningitis. *Brit. M. J.*, Lond., 1915, ii, 604.
- Acute endocarditis.
In: Mod. Med., 2. ed. (Osler & McCrae), Phila. & N. Y., 1915, iv, 148-165.
- Diseases of the arteries.
In: Mod. Med., 2. ed. (Osler & McCrae), Phila. & N. Y., 1915, iv, 449-471.
- Aneurism.
In: Mod. Med., 2. ed. (Osler & McCrae), Phila. & N. Y., 1915, iv, 472-525.

- Raynaud's disease.
In: Mod. Med., 2. ed. (Osler & McCrae), Phila. & N. Y., 1915, iv, 975-997.
- Angioneurotic oedema. Quincke's disease.
In: Mod. Med., 2. ed. (Osler & McCrae), Phila. & N. Y., 1915, iv, 998-1013.
- Diffuse scleroderma. Erythromelalgia.
In: Mod. Med., 2. ed. (Osler & McCrae), Phila. & N. Y., 1915, iv, 1014-1031.
- Osler, Sir W., & Gibson, A. C., Diseases of the valves of the heart.
In: Mod. Med., 2. ed. (Osler & McCrae), Phila. & N. Y., 1915, iv, 212-274.
- Osler, Sir W., & McCrae, T., eds., Modern medicine, its theory and practice. In original contributions by American and foreign authors. 2. ed., v. 4-5, Phila. & N. Y., 1915, Lea & Febiger, 8°.
- Macmichael, William, The gold-headed cane; with an introduction by Sir William Osler; and a preface by F. R. Packard. N. Y., 1915, P. B. Hoeber, 261 p., 8°.

1916

- Science and war; an address delivered at the University of Leeds Medical School. N. Y., 1916, Oxford Univ. Press, 39 p., 8°.
- Discussion on paratyphoid fever. *Proc. Roy. Soc. Med.*, Lond., 1915-16, ix, Med. Sect., 38.
- An address on the tuberculous soldier. *Lancet*, Lond., 1916, ii, 220-221.
- Local tetanus (Correspondence). *Lancet*, Lond., 1916, ii, 877.
- Osler, Sir W., Brown, W. L., [et al.] Discussion on trench nephritis. *Proc. Roy. Soc. Med.*, Lond., 1915-16, ix, Med. & Therap. & Pharmacol. Sect., 1-xi.
- Osler, Sir W., Robb, G., [et al.] Discussion on the treatment of cerebrospinal meningitis. *Proc. Roy. Soc. Med.*, Lond., 1915-16, ix, Therap. & Pharmacol. Sect., 1-26.
- Osler, Sir W., Rolleston, H. D., [et al.] Treatment of cerebrospinal meningitis. *Practitioner*, Lond., 1916, xcvi, 1-18.

1917

- The campaign against syphilis. Delivered before the Medical Society of London. May 14, 1917. *Lancet*, Lond., 1917, i, 787-792.
Also: Brit. M. J., Lond., 1917, i, 694-696.
- The problem of the crippled. Recalled to Life, Lond., 1917, i, 265.
- War wastage: a note of warning to examiners of recruits. *J. Am. M. Ass.*, Chicago, 1917, lxi, 290.
- Recurrence or redeposit of cancer? *Brit. M. J.*, Lond., 1917, i, 455.

1918

- Essai de bibliographie hippique. Edinburgh & Lond., 1918, W. Green & Son, 4 p., 8°.
- The science of librarianship. *Bull. Med. Library*, Ass. Balt., 1917-18, vii, 70-74.
- Typhoid spine. *Bull. Canadian Army M. Corps*, 1918, i, 78-79.
- Graduated exercise in prognosis. *Lancet*, Lond., 1918, i, 231.
- The primary examination for the F. R. C. S. Eng.: an appeal to the President of the Royal College of Surgeons. *Lancet*, Lond., 1918, i, 715.
- Medicine in America (Speech to University Extension Students, summer meeting at Cambridge). *The Hospital*, Lond., 1918, lxiv, 433.
- Trench fever: a critical analysis of the report of the American Commission. *Lancet*, Lond., 1918, ii, 496-499.

1919

- Observations on the severe anæmias of pregnancy and the post-partum state. *Brit. M. J.*, Lond., 1919, i, 1-3.
- Influenzal pneumonia: bilateral rigidity, spinal meningitis with hæmorrhage into the theca vertebralis and nerve roots. *Lancet*, Lond., 1919, i, 501.

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FORMATION OF SINGLE-OVUM TWINS

By GEORGE L. STREETER.

Department of Embryology, Carnegie Institution of Washington

It has recently been the writer's privilege to study the Mateer ovum, a very young, well-preserved specimen containing twin embryos. The larger embryo is in the primitive-groove stage, having an embryonic plate 0.92 mm. long and 0.78 mm. wide. In its form and attachment to the chorionic membrane it is entirely normal and, judging from the best criteria we have at present, it has a development of about 17 days.¹ The smaller embryo consists of an amniotic vesicle 0.1 mm. in its largest internal diameter, and a yolk-vesicle (0.03 mm. internal diameter) slightly detached from it, the two being suspended in the loose mesenchyme in the region of the body-stalk of the co-twin. The position of these vesicles and their relation to the larger embryo are shown in Fig. 1. The chorionic membrane with its villi and trophoblast can be recognized above, while below is shown the yolk-sac of the larger embryo, cut transversely through the region of the body-stalk. Among the loose strands of parietal mesoblast intervening between these can be seen the two detached vesicles which together constitute the very much smaller twin.

The detailed structure of the amniotic vesicle of the smaller embryo is shown in Fig. 2, where its wall can be seen to be made

up of an ectodermal layer clearly subdivided into amniotic ectoderm and a thicker plate below of embryonic ectoderm, which is to form the embryonic shield. The ectodermal layer is everywhere surrounded by an irregular membranous layer of mesoderm. The wall of the yolk-sac consists of a single layer of endodermal cells (see Fig. 3) and, like the amnion, is inclosed in a layer of mesodermal tissue. In general form the amniotic vesicle appears to be normal and corresponds in many respects to those seen in the ova described by Peters, Fetzner, Jung and Strahl-Beneke. It differs from those, however, in being completely detached from the yolk-sac, and in this respect is probably abnormal.

Among the first 2500 specimens in the Carnegie Embryological Collection there are 43 instances of twinning, which is about what would be expected in that number of births if we assume the frequency to vary between 1 and 2 per cent. In nine of these specimens the embryos are not over 20 mm. long—that is, less than eight weeks old—but in only two are they under 5 mm. One of these is the Mateer specimen which I am describing; the other is a pathological specimen (No. 825) which was obtained by Dr. Cecil Vest at operation for tubal pregnancy. In this case the tube contained two chorions undergoing hydatiform degeneration. Sections of these show respective internal diameters of 14 x 12 mm. and 14 x 10 mm.

¹For a complete description of this embryo see "A human embryo (Mateer) of the presomite period." *Contributions to Embryology*, Vol. 9, 1919. Carnegie Inst. Wash., Pub. No. 272.

Neither chorion contains an amnion, and in only one is there any remnant of an embryo (a nodule 2.5 mm. long). In size and character the chorions correspond to those seen in normal ova about four weeks old. The specimen represents, therefore, about the same stage of development as the Watt (1915) twins, in which there were 17-19 paired somites. The Chidester specimen (mentioned by Newman, 1917, p. 68) was at first thought to be twins, one embryo having a development of one month, while the other was supposedly in the primitive-



FIG. 1.—Section of the Mateer ovum showing yolk-sac and body-stalk of the primary embryo, between which and the chorionic membrane are two small ectodermic vesicles constituting the amniotic and yolk vesicles of a twin embryo. $\times 34$.

streak stage. Subsequent study, however, has shown that the smaller structure was not really a twin. If, then, we disregard this specimen, that of Watt constitutes the youngest reported case of human twinning.

The Mateer ovum is considerably younger than the Watt specimen. Whereas the latter is in the stage of 17 somites, the primary Mateer embryo is in the presomite stage and has only just acquired a primitive groove, while the accompanying twin has attained an even lesser degree of development. The fact,

therefore, that it affords the earliest picture of twin formation that has thus far been seen, lends to this specimen a particular interest. Furthermore, it possesses additional importance in that it shows this early stage of the twinning process in a single ovum. Both the Watt specimen and No. 825, mentioned above, are double-ovum twins.

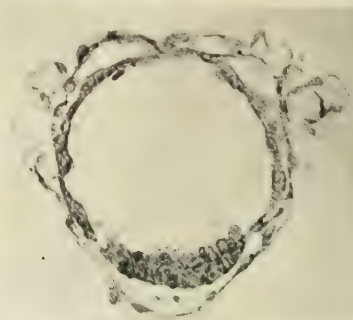


FIG. 2.—Amniotic vesicle of the twin embryo showing the thicker embryonic plate below already differentiated from the thinner amniotic ectoderm. The vesicle is surrounded by an irregular membranous layer of mesoderm. $\times 400$.

The exact character of the mechanism by which human twins are derived from a single ovum is still unknown. There are, however, certain mammals in which polyembryony is the normal occurrence, and where it has been possible to obtain all the stages of the process. This is the case in the nine-banded armadillo which has been carefully studied by Newman (1917) and Patterson (1913). According to these authors, at a time

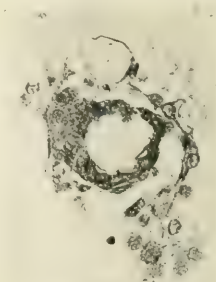


FIG. 3.—Yolk-sac of twin embryo enclosed by an irregular layer of mesoderm. $\times 400$.

when the single amniotic vesicle has reached a considerable amount of differentiation there occurs a physiological isolation of four secondary areas in its wall which undergo independent growth and development, giving rise to four individual embryos with a common amnion. This departs from the conditions existing in human twins, since in the latter there are two separate amnions. This is also the case in sheep.

Very young sheep twins, not more than seven days old, have been described by Assheton. His specimen consists of a blastocyst 0.9×0.7 mm., containing two germinal areas, each apparently perfect and presumably capable of forming a perfect embryo. They were completely separated and in each of them the embryonic mass consisted of a compact cluster of ectodermal cells with a thin endodermal membrane extending a short distance from its margins—the uncompleted yolk-sac. There was a slight difference in size between the two areas and both were smaller than normal germinal areas in the same stage of development. Assheton regarded his specimen as having been produced by fission, or a mechanical splitting apart of the original germinal mass, at the time of the formation of the blastodermic vesicle, which he thinks is rendered more likely in such animals as the sheep, in which the cavity of the blastocyst is produced by an irregular cleft formation which tends to subdivide the embryonic mass. The direction of the line of fission was a matter of concern to Assheton, who thought that only sagittal fission could produce twins and double monsters. Transverse fission separating primary and secondary centers of growth of the embryo he believes to be incapable of producing embryos that would subsequently grow and develop.

Although apparently meeting the requirements in the sheep, it is not probable that this simple mechanical explanation presented by Assheton will be sufficient to explain certain features of the problem occurring in other forms. There is doubtless, as Newman argues, a large physiological element which is not to be explained on morphological grounds. In this connection reference may be made to the interesting experiments of Lewis (1910), who found that small lateral fragments of the medullary plate in the region of the hind-brain, when transplanted, tend to develop individually into a bilaterally symmetrical medulla oblongata, with a characteristic ventricle, roof, and the typical arrangement of white and gray substance. In my own experiments on the otocyst I always found that fractional parts of the otic cup, when transplanted, tend to form completely closed vesicles, although in this organ there is marked predetermination of tissue. We should, therefore, naturally expect that subdivision into two masses of such a primitive and undifferentiated tissue as the embryonic node would result in the formation of two embryos having all the potentialities of the original node.

The earliest stage of development that has been observed in the human embryo is the one described by Miller. In his specimen the embryo, or embryonic node, consists of a solid cell mass undergoing cleft formation preliminary to the opening up of the amniotic cavity. The embryo and the tissue from which the exocoelom is formed are inclosed by a trophoblastic shell of ectoderm possessing irregular syncytial loops which tend to enclose the large blood lacunae surrounding the ovum, there being as yet no villi. This stage is shown in Fig. 5, A. Instead of a single embryo, as was the case in the Miller specimen, the embryonic node is represented as having subdivided into two masses—that is, as having given off a hypothetical twin. It is conceivable that the chances of the

secondary bud reaching maturity would depend upon how large a share of the original mass is contributed to it. If the twin is as large as the primary embryo their chances of developing in an orderly manner would be equal, and this is presumably the case in most instances of identical twins. Where the secondary bud is merely a fragment of the original mass we should expect that, like the fragments of medullary plate in the Lewis experiments, there would be some degree of differentiation; but the process of development would soon be arrested, and at term the stunted bud would be found as a small epithelial cyst on the placenta near the attachment of

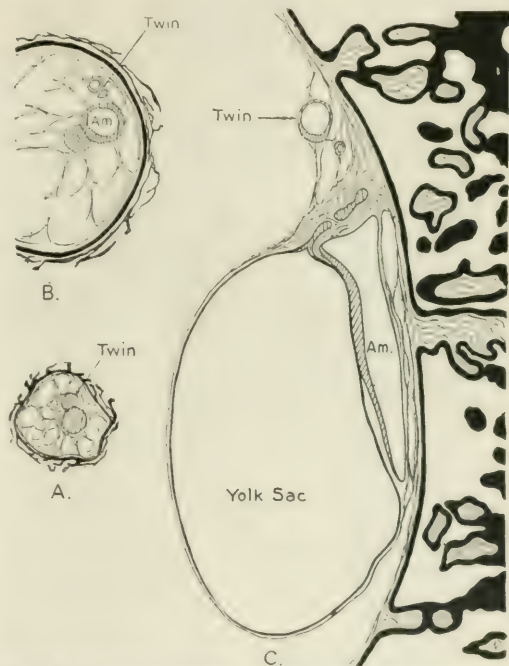


FIG. 5.—Schematic drawing, showing the probable steps in the formation of a single-ovum twin. The stages are drawn at the same scale of enlargement so that they may be directly compared. A. Stage corresponding to the Miller specimen, showing a hypothetical twin budding off from the primary embryonic node. B. Stage corresponding to the Bryce-Teacher specimen. C. The Mateer specimen. The relatively small size of the twin in this specimen, and the detachment of the yolk sac from the amniotic vesicle are indications of arrest in development.

the umbilical cord. In case the twin-bud is only partially detached from the primary node there would exist the basis for the various types of double monsters and teratomata.

A slightly more advanced stage is schematically shown in Fig. 5, B, which may be compared to the conditions existing in the well-known Bryce-Teacher specimen. Here, both embryonic masses have developed into ectodermal (amniotic) vesicles, and at the same time small yolk-sacs are forming near them and probably from cells derived from their wall. The transition from stage B to stage C may be readily followed,

the latter showing the conditions existing in the Mateer specimen. Here the size of the cavity of the yolk-sac has surpassed that of the amnion, a definite body-stalk has formed, and near it are the two vesicles constituting the twin, which, as compared with the primary embryo, is considerably retarded in

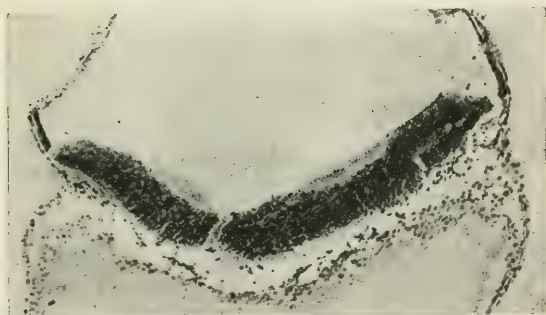
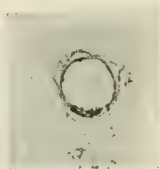


FIG. 4.—Photographs of the twin (above) and the primary embryo (below), taken at the same enlargement (100 diameters) and through similar portions of the embryonic plate.

development. It is probable that under usual conditions the two embryos would be approximately of the same size, and the small size of the twin is to be accounted for by the incompleteness of the bud given off from the primary embryonic node. A comparison of sections made through the amniotic vesicle of

the twin and through a corresponding region of the primary embryo, as shown in Fig. 4, would indicate that the former was essentially normal in form though much retarded in development. The complete detachment of the yolk-sac justifies us, however, in considering it as abnormal. If the pregnancy had not terminated in this case it is probable that the larger embryo would have gone on to maturity and the smaller one would have remained stationary in the form of two minute epithelial vesicles and been entirely overlooked.

In closing I would call the particular attention of obstetricians to this point, for it is probable that a careful search at the placental attachment of the umbilical cord would frequently reveal the presence of similar minute epithelial vesicles, the remains of stunted twins. We might thus find that the tendency toward twinning in man is even greater than is now supposed.

REFERENCES CITED

- Assheton, R., 1898. An account of a blastodermic vesicle of the sheep of the seventh day, with twin germinal areas. *Jour. Anat. and Physiol.*, XXXII, 362.
- Bryce, T. H. and J. H. Teacher, 1908. Contributions to the study of the early development and imbedding of the human ovum. Glasgow.
- Lewis, W. H., 1910. Localization and regeneration in the neural plate of amphibian embryos. *Anat. Rec.*, IV, 193.
- Miller, J. W., 1913. *Corpus luteum und Schwangerschaft. Das jüngste operativ erhaltene menschliche Ei.* Berlin klin. Wochenschr., L, 865.
- Newman, H. H., 1917. The biology of twins (mammals). University of Chicago Press.
- Patterson, J. T., 1913. Polyembryonic development of *Tatusia novemcincta*. *Jour. Morph.*, XXIV, 559.
- Streeter, G. L., 1914. Experimental evidence concerning the determination of posture of the membranous labyrinth in amphibian embryos. *Jour. Exper. Zool.*, XVI.
- Watt, J. C., 1915. Description of two young twin human embryos with 17-19 paired somites. Contributions to Embryology, Vol. 2, Carnegie Inst. Wash., Pub. No. 222.

CHANGES IN SKIN SENSITIVENESS TO TUBERCULIN DURING EPIDEMIC INFLUENZA

By ARTHUR L. BLOOMFIELD and JOHN G. MATEER

(From the Medical Clinic of The Johns Hopkins Hospital and University)

The disappearance of the cutaneous tuberculin reaction in measles was systematically studied in 1908 by von Pirquet¹ following an observation of Preisch.² Fifty-nine children all failed to show skin sensitiveness during the exanthematic stage of the disease. A few observations made at the time of onset showed that the reaction disappeared for from one to four days before the eruption, to reappear gradually after from the fifth to the tenth day. Von Pirquet lays great stress on the specificity of the absence of the reaction in measles, pointing out that it does not disappear in scarlet fever, epidemic meningitis, typhoid fever or German measles. He associates the phenomenon with the tendency of tuberculosis to become more active after measles and explains it by assuming a disappear-

ance of "ergins"—hypothetical substances which unite with tuberculin in the tissues to produce the reaction. Grüner³ performed subcutaneous tests in children with measles and showed that with relatively large doses (1 mg.) a reaction could be elicited even during the eruptive stage. He calculated, however, that the skin sensitiveness was reduced about one thousand-fold. The observation of von Pirquet has been confirmed repeatedly in measles, but we have been unable to find reports of any similar constant abolition of tuberculin skin sensitiveness in other acute infectious diseases except during stages of agonal collapse.

During the recent epidemic of influenza we were struck by the remarkably low leucocyte counts encountered even in mild

or ambulatory cases. This suggested that at least some of the reactive processes of the body were in abeyance. It seemed of interest, therefore, to study skin sensitiveness in this disease. The present report deals with the results of cutaneous tuberculin tests in 19 consecutive cases of epidemic influenza studied in The Johns Hopkins Hospital during January and February, 1919. The diagnosis was based on the symptoms, the presence of hyperemic phenomena of the skin and mucous membranes, the character and duration of the febrile reaction, and the leucopenia.* It should be emphasized that most of the cases were mild and that the disappearance of the skin reaction was in no way associated with general collapse. Three of the patients developed bronchopneumonia, but all made uneventful recoveries. None of them showed clinical signs of active tuberculosis.

Old tuberculin furnished by the tuberculosis dispensary of the hospital was used. Two drops were placed on the forearm about 5 cm. apart. Linear scarification with a dull scalpel was done through the drops of tuberculin after a control scratch had been made distal to them. The tuberculin was allowed to dry on the arm. The tests were all made by the same observers and read at one-, two- and three-day intervals, the character and extent of the redness and induration being noted. Tests were done during the febrile stage and after the temperature had become normal.

RESULTS

The results of the tests are summarized in Table I. It is apparent that skin sensitiveness to tuberculin was absent in every case but one, both mild and severe, during the febrile stage. During convalescence reactivity returned in 89.4 per cent of the cases, which corresponds to what one would expect in a group of normal individuals of the same age. The return to maximum reactivity was gradual in most cases, as shown by successive tests. In two patients a positive skin test was not obtained during the period of observation, even after the temperature had been normal for from six to eight days.

It should be emphasized that, as in measles, more delicate tests, such as the subcutaneous, would probably show reactivity to be simply depressed and not entirely obliterated, and on this basis the cases may be divided into several groups. In ten of them the first test made during the febrile stage failed to elicit any sign of reaction, whereas during convalescence the test was markedly positive. In six cases in which the temperature became normal on the day on which the test was done, or on the following day, slight grades of reddening and induration appeared about the test scratches. These were regarded as delayed and depressed reactions, inasmuch as all these

patients later responded with prompt, strongly positive reactions. It may be that in some of those cases the response was intensified by increased hypersensitiveness following the first test. In one instance of moderately severe typical influenza there was a positive test during the febrile stage. The same degree of reaction was observed in this patient during convalescence.

TABLE I

SUMMARY OF RESULTS OF TUBERCULIN SKIN-TESTS IN EPIDEMIC INFLUENZA

	No.	Per cent.
Total cases studied	19	
Cases giving a positive reaction while fever was present	1	5.2
Cases giving a positive reaction after the febrile stage	17	89.4

Length of time (days) after temperature had become normal before the skin test became positive	Number of cases
1	3
2	4
3	2
4	2
5	3
6	1
11	1

DISCUSSION

Although the literature on alterations of the skin test during acute infectious diseases is meager, it has been generally believed that measles stands out as the only disease in which a constant depression occurs. It is of interest, therefore, to find somewhat similar results in epidemic influenza. Beyond pointing out this fact, it seems difficult to associate the phenomenon in the two diseases, despite certain rather striking analogies which exist between them.* It would seem wise, however, to restudy in detail the changes in skin sensitiveness in other acute febrile diseases, inasmuch as similar conditions may perhaps be found to exist.

REFERENCES

1. Von Pirquet: Deutsche med. Wehnschr., 1908, XXIV, 1297.
2. Preislich: Quoted by von Pirquet, *loc. cit.*
3. Grüner: Münch. med. Wehnschr., 1909, LVI, 1681.
4. Bloomfield, A. L., and Harrop, G. A., Jr.: Bull. Johns Hopkins Hosp., 1919, XXX, 1.

NOTE.—Since this article went to press a paper has become accessible (E. Schiffer: Monatschrift für Kinderh., 1918, XV, 189) dealing with the same question. The writer did skin tests on 64 children with "influenza." In 61 the test was negative, in three it was weakly positive. Of 28 reexamined during convalescence, three developed positive tests.

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HÆMORRHAGE INTO A POSTSCARLATINAL CERVICAL ABSCESS. LIGATION OF THE COMMON CAROTID. RECOVERY¹

By T. M. RIVERS

On December 1, 1916, E. M., of North Carolina, female, five and a half years of age, vomited and had a slight fever. Two days later, a doctor was called, who found her severely prostrated. A small membrane was seen on the right tonsil and 15,000 units of diphtheria antitoxin were given intramuscularly. On December 5, the patient's temperature rose to 101° F., but was normal or subnormal from that time until her admission to the hospital. Her father developed a sore throat one week after the onset of her illness and a culture from his throat was reported positive for diphtheria bacilli by the bacteriologist of the North Carolina State Board of Health. A culture was not made from the child's throat before admission to the hospital.

About December 5, the cervical glands began to swell. The patient again began to vomit, became stuporous and did not pass urine for 56 hours. After this interval, a small amount of urine was passed which contained a great deal of albumin. Her condition remained about the same until the third week, when a diffuse, dull, red maculo-papular rash appeared, three days before admission. She was considered by her physician to have nephritis following diphtheria and was brought to Baltimore to be admitted to the hospital for that reason.

On admission to the Harriet Lane Home of The Johns Hopkins Hospital, December 23, her temperature was 99° F., pulse 110, respiration 22. The patient was drowsy and emaciated. The tongue was heavily coated. The breath was exceedingly foul. Part of the tonsil, soft palate and posterior pillar on the right side had sloughed, leaving a ragged hole lined with greenish-white pus. The glands on both sides of the neck were enlarged. There was a mass the size of a lemon, deeply situated below the angle of the jaw on the right side, that was obscurely fluctuating and was obviously an abscess. The liver was two fingerbreadths below the costal margin. Over the body and extremities there was a worm-eaten desquamation. The skin of the palms and the soles was very dry and later desquamated in a way typical of scarlet fever. There was also a diffuse maculo-papular eruption over the body and the extremities which was evidently urticarial in character.

White blood count, 31,000. Blood culture, no growth. Throat culture, negative for diphtheria bacilli, but showed long chains of streptococci. Urine: clear; acid; specific gravity, 1.020; albumin, 3 gm. per liter; sugar, absent; hyaline and granular casts; pus cells, red blood cells and epithelial cells.

Shortly after admission the cervical abscess was opened by means of a small puncture and at least two ounces of pus were obtained from which a hemolytic streptococcus was grown.

The patient seemed to be doing well until 11 p. m., December 26, when she was found in a large pool of blood, exsanguinated, pulseless and gasping for breath. The bleeding had stopped spontaneously and the wound was not disturbed. A subcutaneous injection of 300 c. c. of physiological salt solution was given immediately and within two hours the patient received intravenously 225 c. c. of citrated blood from the mother.

There was another hæmorrhage of about two ounces at 7 a. m. and at 11 a. m. on the following day. At 1 p. m. blood began to spurt from the wound. Dr. Dandy, the resident surgeon, enlarged the incision into the abscess and found an erosion of the lingual and the external carotid arteries and the internal jugular vein and that the hæmorrhage was from these three sources. A ligature was placed around the common carotid and the bleeding from the internal jugular was controlled by packing. The child was greatly exsanguinated and she received a few moments after ligation of the common carotid 150 c. c. of citrated blood which had been kept on ice since the transfusion the night before. After the transfusion she rallied immediately. Her pulse became very irregular, however, and remained so for two weeks. There was sugar in the urine for one week after the operation, but the blood sugar was always normal.

On December 28 her hæmoglobin was 40 per cent (Sahli). An area of erysipelas developed above the wound and spread over the right side of face. On the 29th she again received 200 c. c. of citrated blood. On the 30th her hæmoglobin was 58 per cent (Sahli). Both ear drums were punctured, releasing pus.

On January 1, 1917, another large hæmorrhage took place through the wound. Evidently the ligature on the common carotid had sloughed through. The bleeding, however, was successfully controlled by pressure and the patient again received 150 c. c. of citrated blood. On January 3 her hæmoglobin was 40 per cent (Sahli).

The patient developed generalized cedema, insensibility to pain, waxy flexibility, Chvostek's sign, a double Babinski, exaggerated reflexes, double ankle clonus and a distinct loss of memory for recent events. Gradually she improved. The wound healed slowly under treatment with Dakin's solution. On January 22, an internal strabismus of the right eye appeared, which cleared up in a week. The patient was discharged from the hospital February 2, 1917, well, with normal urinary findings. She has been heard from several times since and continues well.

Adenitis with abscess formation, especially about the neck, is one of the complications of scarlet fever. At times the blood vessels are eroded and severe hæmorrhages take place. The bleeding may come from an opened abscess or it may occur from the ear or through the mouth and nose. Veins and arteries are

¹ From the Department of Pediatrics, The Johns Hopkins University and the Harriet Lane Home of The Johns Hopkins Hospital.

No.	Name	No. Cases	Vessel	Discussion	Autopsy
1	Syme.	1	?	Bled from ear and mouth; 10 days later common carotid ligated, but bleeding continued at intervals for 3 weeks. Recovery.	
2	Porter.	1	Internal carotid (1)	Blood spurted at times from ear for 4 weeks, resulting in death.	No.
3	Kennedy.	3	Internal jugular (2), 1-1	All died.	2 Yes. 1-No.
4	King.	1	Internal jugular.	Died.	Yes.
5	J. de Bal.	1	Internal jugular.	Died five days after opening of abscess.	Yes.
6	Bloxam.	2	Internal jugular.	Died after bleeding five days. Abscess opened and only blood obtained. Later pus discharged from another opening. Recovery.	Yes.
7	Hughes.	1	External carotid.	Bled from abscess cavity 10 days after it was opened. Common carotid ligated, which controlled the hemorrhage. Child died later.	No.
8	Gordon.	1	Internal jugular.	Died.	Yes.
9	Oshrey.	6	?	Died.	?
10	Blood.	1	?	Died.	?
11	Battersby.	1	?	Died.	?
12	Barrett.	1	Internal jugular.	Bled to death through an abscess cavity.	Yes.
13	Mill.	2	Carotid or its branches.	One died after bleeding through abscess cavity and through mouth. The other bled to death through the mouth.	No.
14	Dépéret.	1	Internal jugular.	Recovered.	
15	Mondière.	1	Branch internal maxillary artery.	Died.	
16	Sedgwick.	1	Internal jugular.	Bled to death in three days.	Yes.
17	Brown.	1	Internal jugular.	Bled to death eleven days after abscess cavity was opened.	Yes.
18	Metcalfe.	?	Internal carotid?	Died.	No.
19	McDonald.	1	Internal jugular.	Died.	?
20	Brown.	1	Artery.	Had three large hemorrhages from mouth.	Yes.
21	Hale.	1	Internal jugular.	Died after bleeding 10 days.	Yes.
22	Nicholls.	1	Internal carotid.	Bled to death in 2 minutes.	Yes.
23	Hymes.	1	Artery?	Bled to death through ear and mouth.	?
24	Häber.	1	Vein?	Tumor mass on side of neck opened. No pus obtained, but child bled to death. Mass was a hematoma.	?
25	Lovegrove.	1	Artery.	Bled to death in a short time through ear, nose and mouth.	No.
26	West.	1	Branch external carotid.	Vessels of neck had been cut by dissection. Died.	?
27	Baader.	3	External carotid. External jugular. Internal sinus.	All died.	Yes.
28	Hansen.	1		Bled about a pint from between the anterior and posterior pillars on left side of throat. Recovered.	
29	Pepper.	2	Artery. Branch of carotid.	Bled through mouth. Recovery after ligation of left common carotid. Hemorrhage controlled by ligation of common carotid. Died.	?
30	Mahomed.	6	?	Two of these cases as Pepper reported. Others died.	?
31	May.	2	Internal carotid. Internal carotid.	Bled from left ear. Left common carotid ligated. Recovery. Bled to death through ear and mouth.	?
32	Hannemüller.	1	Superior thyroid artery.	Bled to death through mouth and nose.	Yes.

involved about equally. Hemorrhage under such circumstances is very serious and few of the cases recover. Most of the authentic cases on record are tabulated here.

BIBLIOGRAPHY

1. Syme: Edinburgh Med. & Surg. J., 1833, XXXIX, 319.
2. Porter: See Kennedy (3).
3. Kennedy: Some Account of the Epidemic of Scarlatina which Prevailed in Dublin, from 1834 to 1842, inclusive; with Observations. Dublin, Fannin & Co., 1843.
4. King: London & Edinburgh Mon. Jour. Med. Sc., 1843, III, 177.
5. de Bal: Jour. d. connaissances médico-chirurgicales, Paris, 1845, XIII, 158.
6. Bloxam: Med. Press, Dublin, 1843, IX, 181.
7. Hughes: Med. Press, Dublin, 1846, XV, 241.
8. Gordon: See Hughes (7).
9. Oshrey: See Hughes (7).
10. Blood: See Hughes (7).
11. Battersby: See Hughes (7).
12. Barrett: Lancet, Lond., 1847, I, 287.
13. Mill: Edinburgh Med. & Surg. Jour., 1841, LV, 125.
14. Dépéret: L'Union médicale, Paris, 1850, IV, 414.
15. Mondière: Revue médicale, 1842, I, 182. Original article not read, reference obtained from: Von Noiro, Histoire de la Scarlatine, Paris, 1847, 216 and 217.
16. Sedgwick: Med. Gaz. Lond., 1851, XLVIII, 581.
17. Brown: Med. Gaz. Lond., 1851, XLVIII, 887.
18. Metcalfe: N. Y. Med. Times, 1852, I, 35.
19. McDonald: See Metcalfe, (18).
20. Brown: Association Med. Jour., Lond., 1854, II, 991.
21. Hale: Lond. Jour. Med., 1850, II, 720.
22. Nicholls: St. George's Hosp. Rep., Lond., 1869, IV, 211.
23. Hymes: Lancet, Lond., 1870, II, 431.
24. Häber: Arch. f. klin. Med., Leipzig., 1871, VIII, 422.
25. Lovegrove: Lancet, Lond., 1870, I, 729.
26. West: See Lovegrove (25).
27. Baader: Correspondenz-bl. f. Schweizer Aerzte, Basel, 1875, V, 614.
28. Rosmer: Bost. Med. & Surg. J., 1878, XCIX, 835.
29. Pepper: Trans. Clin. Soc. Lond., 1883, XVI, 21.
30. Mahomed: *Ibid.* (Discussion.)
31. May: Ann. Surg., 1885, I, 559.
32. Hannemüller: Gefässarrosionen im Verlaufe von Scharlach, Kiel, 1901.

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ANALYSIS OF CEREBROSPINAL FLUIDS OF CATS WITH MENINGEAL INFECTIONS

By LLOYD D. FELTON,
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During the course of the investigation of experimental meningitis in the cat, sufficient data were collected in this laboratory from analyses of cerebrospinal fluids to warrant the publication of a brief report. Our purpose is not only to present the methods used in routine examination, but to provide standards for possible future research on this same problem. A study of the bacteria virulent within the meninges and of the changes in the cerebrospinal fluid caused by such infections will be found in another publication (Felton and Wegefarrth¹). Our chief interest here lies in the choice and application of methods of analysis of the cerebrospinal fluid of normal and diseased animals.

Meningeal infection has long since been recognized by a cellular and protein exudate in the cerebrospinal fluid. With different bacteria as etiological factors, such pathological conditions within the meninges cause also variations in the concentration of glucose, of sodium chloride and of urea, and perhaps other changes both in inorganic and organic constituents. These latter variations, however, aside from the bacteria, are of more theoretical than practical value for the purpose of diagnosis. Reduced to the simplest possible terms, the increased cellular and protein constituents of the cerebrospinal fluid must be considered for our purpose as giving the clearest indication of a reaction caused by the injection of a known micro-organism into the subarachnoid space.

Inasmuch as the etiology in these experimental meningitides is a known factor and is discussed elsewhere, this phase of the question will be disposed of by giving the procedure employed in routine culturing of the cerebrospinal fluid. Since the organisms virulent for the meninges of the cat were easily cultivated, no special bacteriological technique was required to insure growth. Routinely a double meat infusion 0.5 per cent dextrose broth medium, titrated to between Ph. 7.8 and 8, was used. In making the culture of the cerebrospinal fluid, the operator covered the head of the puncture needle with a small fold of sterile cotton; then after the puncture was made, the stylette, with the cotton pledget still intact, was withdrawn and one to two drops of fluid were allowed to escape. Following the escape of these initial drops, from three to eight drops of the fluid were permitted to fall into the culture tube. The top of the test-tube had been well flamed, the cotton plug was reinserted, and the tube entirely cooled just before use. This simple procedure is cited for the reason that but three contaminations occurred in over 2000 cultures, all these during the experiments on the first one hundred animals. Each inoculated culture tube was incubated

for 48 hours and the contents stained. All organisms were identified by appropriate reaction.

The number of white blood corpuscles in the cerebrospinal fluid may be roughly estimated by the turbidity of the fluid. Certainly this is a general rule. In view of the fact that a few red blood cells in an otherwise normal cerebrospinal fluid can easily be mistaken for white cells in a pathological fluid, no specimen was designated turbid without further examination. However, a rather marked difference can be observed in the turbidity caused by red and by white blood cells, respectively. This distinction is brought out in the following manner: When a sample of cerebrospinal fluid containing a few red blood cells (200 to 10,000 per c. mm.) is viewed either by direct or reflected light, it has a velvety appearance. If the tube is twirled, definite cell-eddies with a slight but distinct golden or yellowish sheen can be seen. On the other hand, a cerebrospinal fluid whose turbidity is caused by pus cells, is chalky white and when the tube is shaken, although there are few cell-eddies, the fluid on reflected light is definitely white. Even by these differences in appearance it is not possible, in every case, to distinguish between red and white blood cells. Hence, for accuracy, all fluids were microscopically examined before final classification. This microscopic examination was made in the usual manner. Stained smears were examined for bacteria; cells, stained and unstained, were counted in a double-chambered blood-counting apparatus. A weak solution of toluidin blue proved an excellent stain; this or dilute acetic acid was used.

The methods for the estimation of the protein of the cerebrospinal fluid for experimental work on meningitis leave much to be desired. The well-known clinical tests—those of Pandey, Ross Jones and Noguchi, for example—are at best but roughly quantitative. Though it be granted that they are to some degree quantitative, their strict interpretation depends too largely upon individual judgment. Mestrezat² devised a splendid method for protein estimation which consisted in comparing in standard tubes the turbidity, developed in the cerebrospinal fluid by means of a precipitating reagent, with the turbidity prepared from a known amount of protein. This test would be very satisfactory were it not for the difficulty experienced in preparation and preservation of the standards. In another publication, a method which seemed most suitable for our purpose has been described. Since the technique of this has been slightly modified, it becomes necessary to give the details. It is simply a Micro-Esbach, consisting in the precipitation of the protein of 1 c. c. of cerebro-

¹ Felton, L. D., and Wegefarrth, P.: The Production of Experimental Meningitis by Direct Inoculation into the Subarachnoid Space. Monograph, Rockefeller Institute, 1919.

² Mestrezat, W.: Le liquide céphalo-rachidien, normal et pathologique. Paris, 1912.

spinal fluid in a small graduated tube by means of 0.8 c. c. of Tsuchiya's reagent. The tubes are 4 to 4.5 mm. in diameter and 250 mm. long. The graduations range from 0.5 to 5 gm. to a liter. The tubes were standardized in the following manner: Human serum was diluted with Locke's solution and made to correspond roughly to the percentages desired as measured in a Esbach. This determination was finally corrected by a refractometric estimation. In the small tube to be graduated, each of the protein solutions was precipitated three times and the average level of the precipitation taken to indicate the percentage of that standard solution. Precipitation was allowed to continue for 24 hours before reading. Later in our work the Poca Glass Company of Baltimore prepared, from our standards, tubes on which was marked the height for the cerebrospinal fluid and for the precipitating reagent, in a way similar to that employed for the Esbach.

In the routine estimation of protein, the following technique was employed: By means of a capillary pipette the cerebrospinal fluid is allowed to run into the tube to the mark "Spinal Fluid." Similarly, Tsuchiya's reagent is added to the "reagent" mark. A cork is inserted and the tube gently turned over 10 times, thus causing the bubble of air to thoroughly mix the reagent and spinal fluid, as well as to break up any large clumps of precipitate. The tube is then placed in an exactly vertical position for 24 hours. Precipitation will not be complete if too much protein be present or if the tube be dirty. The best results are always obtained by diluting with normal saline very turbid fluid to one and one-half or more times its volume before putting it into the precipitometer. The tubes are cleaned by inserting a capillary pipette to the bottom of the tube and forcing water through the pipette until all the precipitate has been washed out. Then, with a swab, made by wrapping a bit of absorbent cotton on a small wire, the tube is dried.

Although in this procedure a day elapses before the final reading, this delay is no real disadvantage, for one may as correctly judge the approximate quantity of protein by the number of flocculi produced immediately after the mixing of the Tsuchiya's reagent and cerebrospinal fluid, as by the degree of turbidity developed in the Pandey and Ross-Jones test. In addition, one may have at the end of 24 hours a comparatively accurate idea of the protein-content of the fluid examined. Although an exact estimation of the protein-content of the cerebrospinal fluid is not claimed for this method which gives perhaps an error of 25 per cent, it has proven useful in this series of experiments.

Since Felton¹ has shown that Lange's colloidal gold test is possibly an estimation of the albumin-globulin content of the cerebrospinal fluid, rather than a specific reaction for any one lesion of the nervous system, it was thought advisable to employ the test both as a check upon the protein-content and for the purpose of gaining possible information concerning its specificity. The action was carried out in the classical

way, the gold sol being prepared by a slight modification of Lange's method.² The solution was neutral to alizarin red; 5 c. c. were precipitated by 2.7 c. c. of a 1 per cent solution of sodium chloride; a cerebrospinal fluid from a patient with general paresis gave a typical parietic curve. Each preparation of the solution was also standardized by means of a sample of serum globulin, that is, the globulin solution diluted in Locke's solution until 0.2 c. c. run in the regular test caused a reaction in the parietic zone. This globulin solution was then kept in the ice-box and was utilized to check the sensibility of the sol.

In order that correct conclusions may be drawn in regard to meningeal infection, as it is manifested in the cerebrospinal fluid, the analysis of the normal fluid of the cat must be known. Macroscopically the cerebrospinal fluid of a cat, not differing from that of any other mammal, is a colorless limpid fluid. Microscopically, however, there are a few white blood corpuscles, perhaps 0 to 10 to a c. mm., and occasionally a number of red blood cells.

TABLE I.—NORMAL SPINAL FLUIDS

Animal	Date	Character of fluid	C. c. of fluid	R. B. C. per c. mm.	W. B. C. per c. mm.	Protein grams per liter	Gold sol.
456	4-5-18	Clear	1.5	3	0	0.4	0000111000
449	3-28-18	Clear	1.5	40	10	0.2	0000111000
574	5-8-18	Clear	1.5	20	10	0.6	1122100000
576	5-8-18	Clear	1.0	10	10	0.5	1122100000
583	5-9-18	Clear	1.0	50	10	0.5	1110000000
654	5-24-18	Clear	1.0	0	10	0.15	1222100000
830	6-28-18	Clear	1.0	0	10	0.4	0000000000
715	6-10-18	Clear	1.5	0	0	0.6	0001100000
718	6-10-18	Clear	1.0	0	10	0.3	0110000000
722	6-11-18	Clear	1.5	10	0	0.2	1100000000
758	6-17-18	Clear	1.0	10	0	0.4	0000000000
831	6-23-18	Clear	1.0	0	5	0.3	0100000000
755	6-17-18	Clear	2.0	0	10	0.5	1110000000
740	6-15-18	Clear	1.0	0	10	0.5	1110000000
881	7-5-18	Clear	1.5	2	0	0.1	0011000000
464	4-2-18	Clear	1.5	0	0	0.3	0011000000
674	5-27-18	Clear	1.5	30	20	0.1	1123311000
543	5-29-18	Clear	1.0	5	0	0.5	1110000000
571	3-7-18	Clear	1.5	20	10	0.4	0011000000
757	6-17-18	Clear	1.0	10	10	0.1	0011100000
596	5-14-18	Clear	1.0	10	0	0.5	4532221000

From Table I, one would judge that the cellular element was rather variable, white corpuscles 0 to 20 and red 0 to 50 a c. mm. This table represents the average cerebrospinal fluid of normal cats contained in routine daily occipito-atlantoid punctures rather than the description of the exactly normal fluid. That there are no erythrocytes in the cerebrospinal fluid from normal cats has been demonstrated by the examination of a great number of fluids.

The protein-content varies from 0.1 to 0.6 gm. to a liter. This is rather remarkable and does not accord with the constant amount found to be present in normal human cerebrospinal fluid by Mestrezat,³ and later by Felton⁴—0.25 gm. to a liter. Although we have had a few fluids in which no protein could be demonstrated, a great majority have sufficient to give a precipitate equivalent to between 0.25 and 0.5 gm. to a liter. We consider 0.25 gm. as a low normal and 0.5 gm. as high, bordering on a pathological fluid.

The colloidal gold reaction of these fluids as a rule shows a normal curve. The records from Cats 674 and 596 were exceptions, for in these the cellular and protein elements were

¹Felton, L. D.: A Study of the Specificity of the Colloidal Gold Reaction from the Physico-Chemical Standpoint. Trans. A. M. A., Sec., on Path. & Physiol., 1917, 73.

normal; one a reaction in the luetic zone and the other in the paretic. Our only explanation is that the animals, although they appeared perfectly normal, may have had chronic lesions in the meninges.

The cases of acute meningitis are arbitrarily divided into two classes because of a more complete fluid analysis in one group of animals than in the other. Table II represents a

TABLE II.—ACUTE MENINGITIS.

	No.	Date	Char- acter of fluid	Amount	Cells	Pro- tein	Gold sol reaction
Intravenous injection, 3/14, of B. lactis aerogenes and withdrawal of spinal fluid. Animal died on 3d day.	400	3/14	Clear	1.0	0	5.0	0221000000
	400	3/15	Turbid	.5	14400	60.0	0455533000
Same as 400 except .25 c. c. organisms was given intravenously on 3/15. Animal died on 3d day.	412	3/15	Clear	1.0	0	5.0	0011100000
	412	3/16	Turbid	2.0	1400	6.5	0112344444
Same as 412, injection on 3/17. Animal died on 5th day.	417	3/17	Clear	1.5	100,000	7.0	0111000000
	417	3/18	Turbid	.5	100,000	7.0	0155555555
Subarachnoid injection 2 c. c., 24-hr. dialyate of B. lactis aerogenes on 6/10.	715	6/10	Clear	1.5	0	.6	0111000000
	715	6/11	Turbid	1.0	6000	13.0	5554321000
Subarachnoid injection of 2 c. c. of a 65-hr. dialyate of B. lactis aerogenes on 6/17.	753	6/17	Clear	1.5	10	.2	0000000000
	753	6/18	Turbid	2.0	224,000	4.9	0554433333

well-controlled experiment, both the normal and pathological conditions being present; whereas in Table III the fluids were subjected to at least one characteristic test and found to be normal. It is very probable that the analyses in one group of animals is as trustworthy as in the other. As indicated in Table II, acute meningitis of the cat is accompanied by definite changes in the cerebrospinal fluid; it is turbid, a great number of pus cells are present, the protein-content is increased, and the gold sol reaction denotes abnormality. Cats 411, 412 and 417 were typical clinical cases of acute meningitis—hypersensitive, ataxic, spontaneously crying out as if in pain, and developing acute convulsions on retraction of the head. Animals 715 and 753 were normal on the day following the injection, though possibly a little weak in the hind legs, and at the time of puncture they did not show a clinical meningitis. The first group of animals died and when autopsied were found to have well-marked leptomeningitis; the latter group remained to all appearances normal. From the standpoint of fluid-analysis, the five animals in Table II had definite infective processes in the subarachnoid space. The gold sol reaction of the fluid is interesting. Though all the other findings in the cerebrospinal fluids denoted acute inflammation of the meninges, three of the five produced reactions in the paretic zone. The divergence from the general rule cannot easily be explained. It may be possible that the protein-content in an abnormal cerebrospinal fluid of a cat differs from the human and that there is a relative increase of globulin over the albumin. This last statement has been made in the light of previous work on the explanation of the colloidal gold reaction (Felton¹). It was found that the precipitating factor in the cerebrospinal fluid, if not the globulin itself, was intimately associated with the globulin, in contradistinction to the albumin; this latter as a negative

sol neutralizes the precipitating power of the globulin. The interrelationship of these two substances or proteins, produces the zones in the reactions. If this be true, it is highly probable that in Cats 400, 715 and 753 we are dealing with cerebrospinal fluids containing a greater proportionate amount of globulin over the albumin than in those of Cats 412 and 417.

TABLE III.—ACUTE MENINGITIS

Animal	Char- acter of fluid	Cells	Protein	Gold sol reaction	Injection
359	Turbid	1400	0.9	123455411	Spontaneous meningitis.
420	Turbid	2840	5.0	1123351444	Intravenous mucosus capsulatus and lumbar puncture.
256	Turbid	10000	11.0	0012234433	Subarachnoid, Behring B. coli.
665	Turbid	170	1.4	1245543100	6 c. c. mucosus capsulatus Berkefeld filtrate. Subarachnoid.
758	Turbid	8000	5.5	1112343333	24-hour mucosus capsulatus dialyate.
774	Turbid	...	2.2	1112332211	24-hour mucosus capsulatus dialyate.
270	Turbid	9080	4.0	1233210000	Subarachnoid mucosus capsulatus, 1-12,000.
252	Turbid	9000	9.0	0111244321	Subarachnoid mucosus capsulatus, 1-15,000.
253	Turbid	1800	2.0	0000123210	Subarachnoid mucosus capsulatus, 1-10,000.
254	Turbid	0011244321	Subarachnoid mucosus capsulatus, 1-10,000.
285	Turbid	5.0	0012344221	Subarachnoid mucosus capsulatus, 1-250,000.
596	Turbid	200	4.0	1335555555	Intravenous mucosus capsulatus, occipito-atlantoid puncture.
417	Turbid	100,000	6.0	0123555555	Intravenous mucosus capsulatus, occipito-atlantoid puncture.
684	Turbid	1600	2.0	2455832110	Mucosus capsulatus, Berkefeld filtrate, 72 hours.
755	Turbid	2.0	1112355532	Mucosus capsulatus, Berkefeld filtrate, 24 hours.
764	Turbid	7160	4.5	1113444332	Mucosus capsulatus, Berkefeld filtrate, 72 hours.

All of these animals (Table III) were given direct subarachnoid injections with micro-organisms or with filtrates or dialyzates prepared in one way or another from micro-organisms. And although most of the animals developed an acute and fatal meningitis, confirmed at necropsy, a number not only survived, but were not noticeably affected. Nevertheless, in view of the reaction of the meninges as evidenced in the cerebrospinal fluid, all can be classified as cases of acute meningitis. The gold sol test in this group of cases is not so atypical as in the former group—the reaction taking place more characteristically in the meningitic zone. However, in animal 270 the gold sol reaction was exhibited in the luetic zone. Comparing Lange's test in the two groups of acute meningitides, it is evident that the cerebrospinal fluid of animals having acute meningitis does not cause a differential zone reaction, the curves occurring in any of the three regular zones.

The cerebrospinal fluid of a cat having chronic meningitis varies only slightly from the fluids obtained in that disease in the human subject. As can be seen from Table IV the character of the cerebrospinal fluid changes from turbid in the acute or subacute stage of the disease to clear in the definitely chronic condition. The number of pus cells and the amount of protein vary in about the same relation—a gradual decrease in both elements. The gold sol reaction is very remarkable.

In the acute stage of the disease the cerebrospinal fluid exhibits the average reaction with all the tests for that condition. But with one exception (293) the gold sol reaction takes place in the paretic zone. For instance, Cat 211

with a turbid fluid, containing 800 pus cells, 10 grams of protein to a liter and giving a reaction in the meningeal zone with the gold sol test, was sick for over two months (finally sacrificed because of its weakness) and a month before death the cerebrospinal fluid was normal except for three (blue) reactions in the paretic zone with Lange's test. Better

TABLE IV.—CHRONIC MENINGITIS

Clinical course of animal	No. of animal	Date	Char-acter of fluid	Cells	Pro-tein	Gold sol reaction
Subarachnoid injection of 1 c. c. Streptococcus meningitis on 12/27. For 3 weeks cat seemed normal. On 12/31, the disease had weakly returned but up to 1/1 when it became more marked and was practically normal 1/9. Animal was transferred 3/6. Culture of spinal fluid was negative throughout.	165	12/27 12/29 2/22 3/6	Clear Clear Clear Clear	0 80 21	0 0 0 0	0011210000 0001121000 0001121000 0001121000
Subarachnoid injection of 1 c. c. B. coli, No. 9, 1/24 normal active animal throughout the entire period of observation. Positive culture of spinal fluid 1/26 and 2/4, negative 2/19.	453	1/29 2/1 2/7 2/19	Turbid Turbid Solution turbid 40 ..	3.0	0012345555 0012345555 0123210000 311210000
2/8. Subarachnoid injection of 2 c. c. streptococcus meningitis on 2/8. For 2 weeks cat seemed normal. On 2/21, culture of spinal fluid 2/21 normal.	169	2/8 2/11 2/21	Clear Turbid Turbid 512	.. 1.5 ..	0011101000 0013310000 0013310000
2/27. Subarachnoid injection of streptococcus from autopsy No. 3458. Chronic state represented by refusal to eat, weakly active, with some macroscopically of meningitis. Dura lost its luster. Markings in cord indistinct.	328	2/28 3/1 3/16 3/21	Turbid Turbid Solution turbid	2200 540 90 20	2.5 2.0	0010910000 0124132100 0013310000 0013310000
Subarachnoid injection of cat streptococcus 1/29. Quite weak the next day. The cat became thinner, weaker, and more ataxic up to its death 4/16. (Sacrificed with ether). 2/5. Culture was positive for streptococcus, negative afterward.	311	1/30 2/5 2/8 3/8	Turbid Turbid Turbid Clear	800 .. 400 ..	10.0 5.0 .. 0.2	0012341444 0012345555 0012345555 0012345555
Subarachnoid injection of pneumococcus 2/19. Cat was quite sick for 7 or 8 days. Became active and normal 3/5.	260	2/19 3/5	Turbid Clear	1440 90	9.0 ..	0000010000 0013310000
After subarachnoid injection of B. typhosus 12/31, developed very marked acute meningitis changing into subacute and chronic in 2 months. Sacrificed 4/21. Autopsy showed chronic process over hemispheres.	124	2/11	Clear	10	..	0012100000
Chronic pneumococcus meningitis 31/2 months.	107	1/29 3/6	Clear Clear	90	0014010000 0014010000
Acute streptococcus meningitis for 10 days, then normal active animal from 2/22 to 3/11.	309	3/6	Clear	0012100000
Subacute meningitis at autopsy. B. gallinarum 1 month's duration.	134	2/4	Clear	214	..	0012100000
Subarachnoid injection 1 c. c. 1-400 B. coli, Behring. 2/25. Acute meningitis over period of a week. Normal active animal after 8 days.	310	3/12	Clear	0012100000
Subarachnoid injection 3/1, 1 c. c. 1-400 B. coli, Behring. Normal active animal after 8 days.	315	3/21	Clear	0012100000

examples of this change are found in Cats 134 and 310. Each of these, though examined but once, show a cerebrospinal fluid that is almost typical of the one found in general paresis—a clear fluid, having 214 cells, with a slight increase in the protein-content and an exact representation of a paretic zone reaction. Possibly our best clinical example of chronicity is Animal 124, which showed at necropsy a typical chronic meningitis. For two days after the initial subarachnoid injection

of 1 c. c. of a 24-hour broth culture of *B. typhosus*, the animal was drowsy, had a wobbly gait, reacted as if to pain on retraction of head, and refused to eat. Unfortunately there were too many erythrocytes present in every cerebrospinal fluid obtained, except the one given in Table IV, to make a complete record. *B. typhosus* continued to be present in the cerebrospinal fluid for one month as determined by cultures. Clinically, the drowsiness gradually cleared up, the animal's appetite returned slowly, but it remained sick. The gait changed from an ataxia to an almost complete paralysis of the hind legs. Its condition became progressively worse so that it was sacrificed at the end of two months. The heart's blood and cerebrospinal fluid cultures were negative at necropsy. A similar case, but with complete cerebrospinal fluid analysis, is found in Animal 328. Were it not for the clinical picture of an acute onset developing into a chronic state (weakness, loss of appetite, ataxic gait, etc.) one would be justified in diagnosing the case as a normal recovery from an acute meningitis. A culture of the cerebrospinal fluid was negative on the sixteenth day.

The reversal of the zone reaction of the Lange's test parallel to the development of a chronic state in the animal is of more than passing interest. We have an acute irritation of the meninges with a characteristic exudate (Animals 328, 211, 169) slowly subsiding and becoming, as far as we are able to tell from the cerebrospinal fluid, almost normal. Accompanying this is a gradual decrease in the precipitating factor of the spinal fluid in the colloidal gold test with a change from a meningitic to a paretic reaction. Many possibilities suggest themselves in explanation. Granting that the precipitating agent of the cerebrospinal fluid is globulin, the question as to the source of this protein naturally arises. Are we dealing with a residual globulin from the acute inflammation of the meninges; have the meninges so changed in character that albumin is allowed to pass and globulin is not (a thing that is not possible *in vitro* when a dialyzing sack is used); is the globulin of the central nervous system thrown into solution in a process of gradual degeneration; or do the micro-organisms synthesize a globulin by their growth?

The similarity of the zone reaction in chronic meningitis of the cat to the reaction given in general paresis in man leads us to ask whether the cerebrospinal fluid of any chronic lesion of the nervous system will produce a paretic curve. That this occurs in some cases, at least, of multiple sclerosis, brain abscess, chronic lead poisoning and paralysis agitans, is well known. It is probable that other chronic diseases of the central nervous system will cause a reaction in the paretic zone, if the examination be made at the proper time. It is not our purpose to belittle the value of the test in general paresis provided the Wassermann reaction be done at the same time, but the importance of care in interpreting reactions of the paretic zone should be emphasized.

SUMMARY AND CONCLUSIONS

I. A method is given for the measurement of protein in the cerebrospinal fluid. It has been found to be of as great value in acute meningeal infections as the Pandy or Rose Jones tests in

differentiating the cerebrospinal fluid of normal cats from those with chronic lesions in the central nervous system.

II. The normal cerebrospinal fluid of a cat contains 0 to 10 white blood corpuscles per cubic millimeter, from 0.1 to 0.5 gm. of protein to a liter, and gives a negative curve in the colloidal gold reaction.

III. The cerebrospinal fluid in acute meningitis of a cat has been found to contain from 200 to 22,400 white blood corpuscles, 2 to 17 gm. of protein to a liter, and to give a reaction in any of the three zones in the gold sol test.

IV. The cerebrospinal fluid of chronic meningitis of a cat is practically normal with exception of the gold sol reaction, a change to the paretic or to the luetic zones has been

recorded. There may be a slight increase in the number of white blood corpuscles and in the content of protein.

V. The colloidal gold reaction has been of service in demonstrating a pathological cerebrospinal fluid, but has shown no specific zone reaction, except to a slight extent in the cerebrospinal fluids from animals with chronic meningitis.

VI. There was indeed a great similarity in the Lange's test as applied to the cerebrospinal fluids from cases of experimental chronic meningitis, and those of general paresis in human patients. It was suggested that the paretic zone or even the luetic zone reaction denotes, where there is a small amount of protein present, merely a chronic lesion of the central nervous system.

HORACE GREEN AND HIS PROBANG¹

By WILLIAM SNOW MILLER,
University of Wisconsin

One of the interesting episodes connected with the history of American medicine is associated with the name of Horace Green who, in 1840, announced that he was able to pass a sponge-tipped probang into the larynx and thus apply medication directly to the laryngeal mucosa, and even to that of the trachea. The stormy discussion occasioned by this simple statement extended over a period of 19 years and spread beyond this country to England and France.

Horace Green was born in Chittenden, Vermont, December 24, 1802, and died at his home at Sing Sing, now Ossining, New York, November 29, 1866, in the sixty-fourth year of his age. His father was one of four brothers, sons of a Massachusetts physician, who served in the Revolutionary War. Two of them fell with Warren at the battle of Bunker Hill; the third fell in the battle at Monmouth; the fourth fought through nearly the whole of the long struggle and raised four sons, the youngest of whom is the subject of this sketch.

Horace Green studied medicine with his brother Dr. Joel Green, of Rutland, Vermont, and graduated at Middlebury, Vermont, in 1824, from the institution known later as the Castleton Medical College. The succeeding five years he spent in partnership with his brother, and in the fall of 1830 went to Philadelphia where he attended lectures at the medical department of the University of Pennsylvania. In the spring of 1831 he returned to Rutland where he continued in practice until 1835 when he removed to New York City.

In 1838 he spent some months in Europe, and on his return, late in the year, began at once his investigations into the pathology and treatment of diseases of the throat.

From 1840 to 1843 he was connected with Castleton Medical College as professor of medicine and as president of the institution. In 1850 he helped to found the New York Medical College. Here he occupied the chair of theory and practice of medicine and was elected president of the faculty and also of

the board of trustees. In 1860 he retired from active service and was made emeritus professor. In 1854 he, and his colleagues, founded the American Medical Monthly. Dr. Green was A. M. (honorary) from Union College; LL. D. from the University of Vermont; Phi Beta Kappa and a member of the Society of the Cincinnati.

In the Boston Medical and Surgical Journal, Volume XLII, 1850, a good pen picture is given of Dr. Green. He is described "as tall and rather spare; very black hair, now a little grey; a sharp black eye, rather a brunette; and gentle and kind in his address. His manners are quiet and dignified, those of a gentleman accustomed to good society. They say a poet must be born. Cato [*nom de plume* of the author] opines that this is equally true of a gentleman; and he further thinks that nothing so deforms a man, especially a medical man, as rough or clownish manners. If any man should be gentle, in the highest sense of the word, it is he who ministers to our diseased bodies and minds." The account closes "long may he live to enjoy the honors and emoluments of the profession which he has well and truly labored in."

In the obituary notice of Dr. Green published in the New York Medical Journal, Volume IV, 1886, it is stated: "Few men in the profession of medicine in this country have attracted so much attention to their professional career as did Dr. Green. Announcing, in his earlier writings, a plan of treatment for diseases of the air passages which was at once regarded as 'bold and novel,' it met, naturally, much skepticism and opposition. This induced investigation into the subject in dispute. An impetus was given to the study of laryngeal diseases, and, as a result, the means of their diagnosis and treatment have been immeasurably increased. Dr. Green lived to see the views he promulgated thoroughly proved by the aid modern science has placed in our hands."

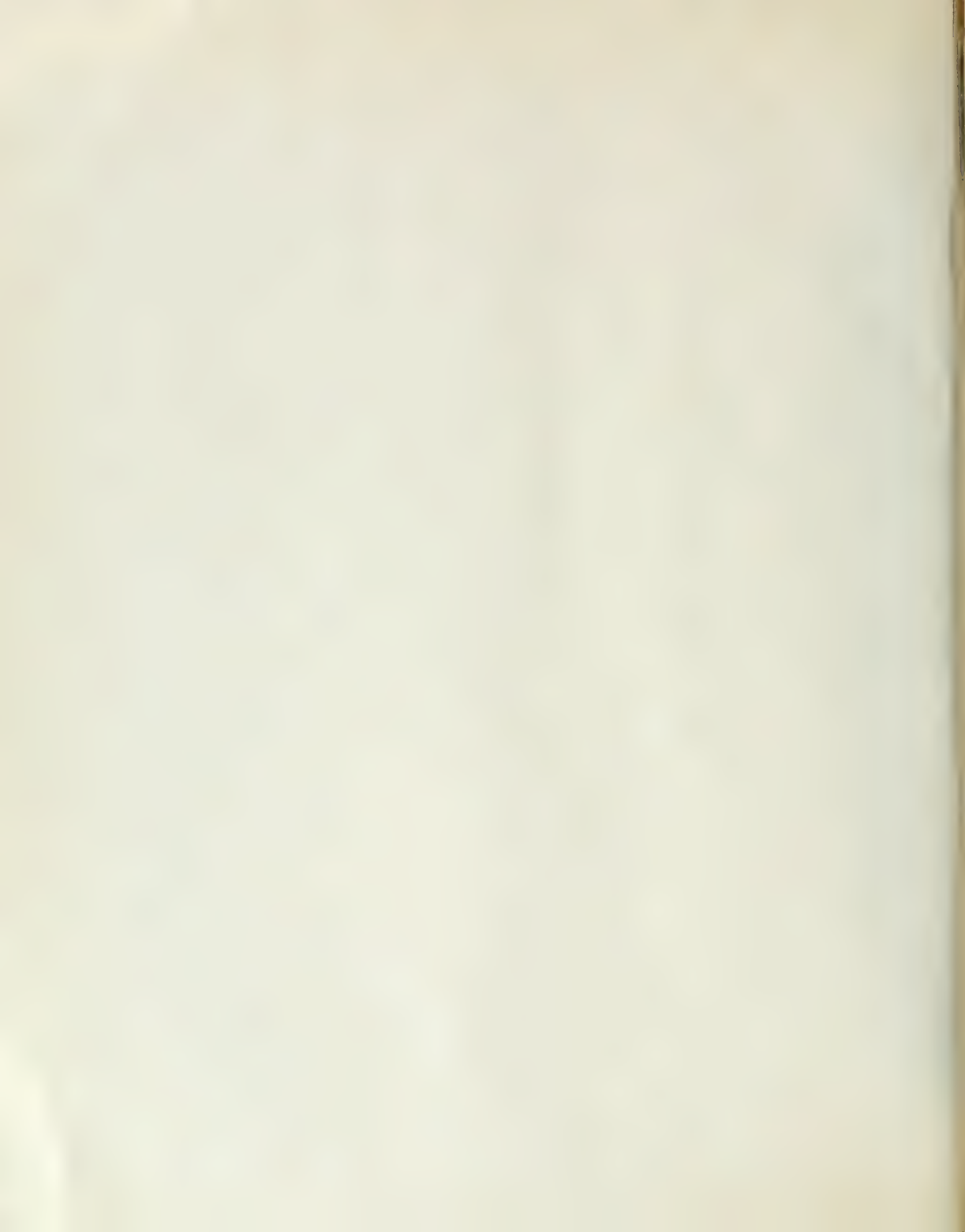
Horace Green published his "Treatise on Diseases of the Air Passages" in 1846. In the introduction to this work he says: "More than six years ago, namely, in 1840, I brought before the New York Medical and Surgical Society, . . .

¹ Read before the Wisconsin Medical History Seminary, 1916-1917 session. Read before the Historical Club of The Johns Hopkins Hospital, May 26, 1919.



HOWARD GREEN

Enlarged from a small card photograph in the Howard A. Kelly collection of portraits at the Johns Hopkins Hospital. This was taken probably about 1855.



the subject of the treatment of diseases of the larynx, by direct application of therapeutical agents to the lining membrane of that cavity. . . . Such, however, was the degree of skepticism on this subject, manifested, at the time, by a large proportion of the members, that for many years I have refrained from bringing the matter again before the society."

The first three chapters of the book deal with the anatomy and pathology of the throat, larynx and bronchi. In the fourth chapter the main purpose of the book is stated when emphasis is laid on the mucous glands and follicles "scattered along the extent of the lining membrane of the respiratory tubes." When these are affected they give rise to that affection of the throat which is called "bronchitis"; "chronic laryngitis"; "clergyman's sore throat," and is frequently found among public speakers and others. "The structural changes, to which the mucous follicles of the throat and air passages are liable, are: Inflammation, which may result in ulceration, hypertrophy, induration, or in a deposition of tuberculous matter in the follicles themselves; attended, in most of these conditions, by a greatly increased, and vitiated, mucous secretion."

"The disease of the mucous glandulae may be primary, and uncomplicated, and be limited, entirely, to the fauces and pharyngo-laryngeal membrane; or, it may be complicated with hypertrophy, and induration of the tonsils, and with elongation of the uvula. It may accompany, or be consecutive to, other affections of the air passages, and co-exist with laryngitis, bronchitis, or with pulmonary phthisis."

Among the causes of "follicular diseases" or, as we now term it "follicular pharyngitis" or "granular pharyngitis," Green enumerated climate, age, influenza, sudden strain of the voice in public speaking and tobacco. Valentine Mott, on his return from his European trip, said that the reason why clergymen on the other side of the water were so free from "sore throat" was their free use of "the weed." I am afraid I shall have to agree with Mott. The assignment of influenza as an exciting cause is, I think, agreed to by most of us from personal experience.

I pass over much that is of interest in the volume, mentioning only his illustration of œdema of the uvula which occurred in a case where suffocation was nearly caused, in two instances, by its being aspirated into the glottis, and take up Green's method of treatment. He did not neglect constitutional remedies when he considered them serviceable; his chief method of treatment was, however, the application, by means of a sponge-tipped probang, of a solution of silver nitrate, which varied in strength from two to four drachms of the crystals to the ounce of distilled water. He lays emphasis on the use of the solution of the pure crystals rather than the solid nitrate. In some cases where extensive ulceration was present he did not hesitate to apply a solution of double the last-mentioned strength. The silver, he says, "does not act, as has been supposed, by burning, or by destruction of textural matter: it forms, immediately an union with the albumen, and other secretions of the mucous lining, and this compound, thus formed, defends the living tissue from the action of the

caustic; whilst it operates to produce a most favorable change, in the vital actions of the parts."

Green laid a great deal of stress on the proper education of the larynx in order that the probang could be properly, and with as little difficulty as possible, introduced into it. Disregard of this point caused numerous failures, as we shall see later, by the committee who investigated his method of treatment. The larynx should not be entered at the first sitting, but the solution should be applied about the epiglottis and pharyngeal region on several successive days before this is attempted (this was before the days of cocaine).

The directions for passing the probang are explicit. "The instrument being prepared, and the patient's mouth open wide, and his tongue depressed; the sponge is dipped into the solution to be applied, and being carried over the top of the epiglottis, and on the laryngeal face of this cartilage, is suddenly pressed downwards and forwards, through the aperture of the glottis, into the laryngeal cavity" (the laryngoscope had not as yet come into use).

The year following the publication of Dr. Green's work on "Diseases of the Air Passages" there appeared in the Boston Medical and Surgical Journal a most bitter and, as later events showed, unwarranted attack on Dr. Green and his book. The book is designated as "a misnomer, for nothing whatever either novel, important or useful, is even suggested in relation to 'bronchitis.'" The whole ten chapters are made up of a dissertation upon follicular disease." The reader "will expect to find the proofs that the novel feat of passing an armed probang, through the larynx, into the trachea down to the bifurcation, has been performed, thus curing bronchitis by the topical application of his curative means to the inflamed membrane. It is this monstrous assumption which was scouted by the profession, as 'ludicrously absurd, and physiologically impossible.'"

The author of the article in question states that in all probability the armed probang entered the œsophagus and on its withdrawal some of the contents of the sponge "has descended into the laryngeal cavity." The article goes on to say "he has the name of having accomplished, what the profession declared to be impossible, by swabbing out the larynx, trachea and bronchi themselves."

But the author brings a still more serious charge against Dr. Green—plagiarism. Trousseau and Belloc published in Paris, in 1837, a work entitled "*Traité pratique de la phthisie laryngée*." This was translated into English and published in Philadelphia in 1839; this is the work that Green is charged with plagiarizing. Green had affirmed that he had been using his method of treatment for two years before he heard of Trousseau and Belloc; but the author scorns his statement saying that as Green was in London in 1838, it was impossible for him not to have heard of Trousseau and Belloc.

Let us see what Trousseau and Belloc have to say on the subject and if they really did enter the larynx for the direct application of medication. They first describe the bending of a piece of whalebone and the tying on of a small piece of sponge which they moisten with a solution of nitrate of silver. With

the mouth open, and the tongue depressed, they introduce the armed probang. "When the isthmus of the gullet is passed, there occurs an effort of deglutition which elevates the larynx, and we seize this opportunity to draw forward the sponge, which had been at the entrance of the œsophagus. By this manœuvre we get the glottis, and it is easy to express the solution into the larynx; the cough which now occurs favors the introduction of the caustic." This is quite another thing from entering the larynx and applying medications directly to the parts as Green claimed to do; moreover, Trousseau later was exceedingly skeptical of the assertion made by Green that the larynx could be entered, but finally, in 1858, he acknowledged that Green had actually accomplished this feat. The relation between the two men was always a pleasant one and we find Trousseau sending patients to Green for treatment.

An extended review of Green's book is also found in the *New York Journal of Medicine*, Volume VIII, 1847, in which Green is highly complimented for the work he has accomplished and the advance he has made in the treatment of laryngeal affections, but the reviewer fails to distinguish between the expression of medication from a sponge-tipped probang and the passage of a sponge-tipped probang into the larynx thus applying the medication directly to the mucosa.

In 1851 Green returned from a second visit to Europe and we now find that the discussion of his method of treatment has extended to the other side of the Atlantic, for Erichsen, in his "Science and Art of Surgery," London, 1853, declares that "Not only does physiology and ordinary experience tend to disprove the possibility of such a procedure, but repeated experiments, both on the living and on dead subjects, have led me to the conclusion that it is utterly impossible to pass a whalebone, whether curved or straight, armed with a sponge, beyond, or even between, the true vocal chords."

On the evening of December 6, 1854, Green read before the New York Academy of Medicine a paper entitled "On the Employment of Injections Into the Bronchial Tubes, and Into Tubercular Cavities of the Lung." In this paper Green reviews the work he has accomplished and gives additional cases which have been successfully treated. He also mentions by name numerous well-known physicians who had used his method successfully. Marshall Hall, an eminent physiologist of his day, about this time was on a visit to this country and the scene for the moment shifts to Chicago. Like Erichsen, Marshall Hall believed that the introduction of "a sponge wet with the caustic solution into the larynx and trachea, as proposed, would prove fatal to animal life." He was won over to Green's support by seeing Professor Brainard introduce a tube into the trachea of a dog, and afterwards by seeing Green perform the operation of cauterizing the larynx and trachea at his office in New York. Marshall Hall's renunciation of his former position can be found in the *Northwestern Medical and Surgical Journal*, Volume II, N. S.

It was Marshall Hall who suggested to Green the use of a tube and the passage out of it of the expired air as a proof of tracheal catheterization. Green accordingly procured a number of Hutchings' flexible tubes and attaching a sponge, the

size of that used by him in ordinary practice, to the extremity of one which was 13 inches long he introduced it into the trachea of a patient.

"On withdrawing the wire the patient was directed to blow and breathe through the tube. This he did for several moments filling and emptying the chest of air repeatedly. A lighted lamp was then brought, and this was extinguished promptly, several times, by blowing through the tube." In still another test a bladder was tied to the free end of the tube and it was inflated and collapsed a dozen times. These and numerous other experiments are described by Green in his paper to prove that he was able to enter the larynx for the direct application of medication.

The paper is lengthy and I cannot improve on the summary given by Fordyce Barker in his report to the New York Academy of Medicine. He states that Dr. Green's paper contains the following three distinct propositions:

1st. That direct medication of the lungs, by means of catheterism of the air tubes, has not before been accomplished.

2d. That the operation may be performed by the dexterous surgeon with ease and facility, and with perfect safety to the patient.

3d. That the results of this method of treating disease, whether it is employed in bronchial affections or in the commencement of tuberculosis, have already afforded the most gratifying indications that practical medicine will be advanced by this discovery.

A committee of seven was appointed by the academy to "investigate the treatment proposed by Dr. Green in his paper read this evening." The committee consisted of Drs. Willard Parker, chairman; Isaac Wood; James Anderson; John O. Stone; B. Fordyce Barker and J. T. Metcalf. After a delay of six months this committee reported Wednesday evening, July 18, 1855. Two reports were submitted; a majority report signed by Drs. Parker, Stone, Wood and Metcalf. The minority report was submitted by Dr. B. Fordyce Barker. Drs. Anderson and Stevens did not sign either report, but sent letters to Dr. Parker, the chairman, stating that they did not think the committee had given sufficient investigation to some of the features of the report or that they were not fully convinced in regard to the practicability of introducing the probang into the trachea. The conclusions of the majority report are as follows:

1. Catheterism of the air-passages dates its history from the time of Hippocrates.

2. The best evidence of the presence of an instrument into the air-passages are the rational signs.

3. The facility of the operation depends upon the kind of instrument used; the tube having a large curve being the best, and the sponge probang least adapted to enter the trachea.

4. That there is no reliable evidence, in the opinion of your committee, that the sponge probang has been passed through and beyond the vocal chords.

5. That there is no positive evidence that an instrument can be passed at will into the right or left bronchial divisions.

6. That, in the great majority of instances, where injections are supposed to have been thrown into the lungs through a tube, they have passed directly into the stomach.

7. That, as regards the utility of injections of nitrate of silver into the lungs, the facts thus far developed in the experiments of

your committee lead them to regard the operation as one attended with danger as well as difficulty.

The minority report sets forth the duties of the committee as follows:

1st. To ascertain whether direct medication of the lungs, by means of catheterism of the air tubes, has been before accomplished.

2d. To ascertain whether the operation may be performed by the dexterous surgeon with ease and facility, and with perfect safety to the patient.

3d. To ascertain, as far as possible, the therapeutic results of this treatment.

The following extract from the records of the secretary of the committee is quoted in support of this position:

It was concluded, after some general discussion of the subject, that the committee should endeavor, first, to settle the question of the passage of the tube into the trachea; and as far as possible, to ascertain the utility of the injections of nitrate of silver into the lungs.

Although Dr. Green insisted that the throat should be properly educated before attempting to pass the probang, the committee disregarded the purpose for which they had been appointed and spent a considerable amount of time in attempting to pass the sponge probang without any previous preparation of the patient and in a very crude manner, as will appear later. Dr. Green himself failed to pass the instrument in some cases, when the committee requested him to make the attempt, from this very cause; but in one instance in which he passed one probang into the trachea and a second one into the œsophagus, moving the one in the œsophagus up and down produced no motion by the first; nevertheless, Dr. Parker was not convinced that the first was in the trachea.

The statement made by the majority report that "catheterism of the air passages dates from the time of Hippocrates" was called in question by Dr. Barker and it may still be called in question by the student of medical history.

The full minority report, like the majority report, was lengthy, and I will give the conclusions presented to the academy:

1st. Direct medication of the lungs by means of catheterism of the air tubes, was first proposed and carried out by our associate member, Dr. Horace Green.

2d. The operation may be performed by the dexterous surgeon, with ease and facility, and with perfect safety to the patient.

3d. The results of this method of treatment, whether it has been employed in bronchial affections or in the commencement of tuberculosis, have already afforded the most gratifying indications that practical medicine will be greatly advanced by this discovery.

In the discussion on the reports of the committee, Dr. McNulty made the statement that as the result of many dissections he was able to prove that it was an anatomical impossibility to enter the larynx. This he proceeded to demonstrate by various diagrams and preserved specimens.

To this Dr. Sayre replied saying that "he was amazed that any man should come before the academy with a drawing and attempt to prove that it was an anatomical impossibility to enter the larynx, when every surgeon had been called upon to remove foreign bodies from the air passages; and if foreign

bodies can get there by accident, why cannot the surgeon pass instruments intentionally?"

Dr. A. K. Gardner called attention to the well-known fact that, in the disease of chickens known as "pip," blunt-pointed wires armed with a pledget of cotton dipped in turpentine are passed into the trachea. The natural inference from his remarks would be that, if it is possible to pass the glottis in the lower animals, it is also possible in man.

Well did Dr. John Shanks say "The subject of discussion this evening is one, which, if precipitately acted upon by this academy, may, perhaps, cause many hereafter to regret, that they had not more deliberately, more perseveringly, and upon a larger and more extensive basis of tests and experiments, founded their opinions." After referring to the "hue and cry" that was raised against Horace Green when he first announced that he was able to enter the larynx and that since then his statement had been frequently confirmed, Dr. Shanks goes on to say, that he is "not at all surprised that the English and French allies, Professors Erichsen and Trousseau, are still before the walls of Troy." In other words they had not as yet acquired the necessary skill to pass the probang. Continuing, Dr. Shanks says: "I remember, many years ago, listening to a lecture delivered to his class, by the distinguished and learned chairman of the committee of this report. He was speaking of the introduction of the male catheter into the bladder, and in the course of his remarks took occasion to eulogize the practice of a Parisian surgeon, for the skill, rapidity, and address with which he performed this simple operation; and to say that it alone was worth a trip to Paris, to witness his execution of it. I must conclude, then, that that estimable gentleman, the chairman of the committee, has faith in the possibility of acquiring an eminent degree of skill and address in the use of catheters. Why, then, I would respectfully enquire, was there no allusion made to the possibility of the possession of this accomplishment by many of his contemporaries at home, in the catheterization of the air passages—a far more nice and intricate operation; and presenting a field equally as interesting, and less explored, for the exercise of American genius and talent; which—I may say without any sacrifice of modesty, as I am not a native born American—is second to none on the civilized globe?"

There was a good deal of haggling over the curve the probang should have in order to enter the larynx easily; for it was acknowledged that in some instances it did enter the larynx. The original curve as described by Horace Green was "one which will form the arc of one-fourth of a circle, whose diameter is four inches." The committee decided on a six-inch curve. Green, himself, stated that, although the four-inch curve made the introduction of the probang into the larynx more certain, it did not permit the passage of the probang beyond the vocal chords. He therefore lessened the curve and finally found that "by having the head of the patient thrown well back, so as to bring the mouth as near as possible on a line with the opening of the glottis, an instrument with the small curve, or nearly straight, may be introduced any required distance into the trachea with much ease, and ordinarily, with

much certainty." This position of the patient and form of probang permitted also the entrance of the probang into either bronchus.

When we compare this statement of position with that used by Brünings, for example, we see how far Horace Green had advanced in his technique. Moreover, entrance into the subdivisions of the bronchial tree can be actually demonstrated with the modern laryngoscope, and Brünings describes a case in which he passed a lead-tipped probe 2.5 mm. in diameter, a distance of 38.5 cm. and then made a röntgenogram of the probe *in situ*.

It was brought against Green that he stated that he could inject the bronchi and tubercular cavities in the lung. The experiments with the flexible tube, suggested to Green by Marshall Hall, led him to go a step further and, after introducing the tube, inject through the tube the solution of silver nitrate into the lung. The success attending this procedure suggested to the active mind of Green a possible treatment of tubercular cavities. I am unable to find in any of his published works, so far as they are available to me, a statement that he had made the attempt. He himself says that he had never made any such claim. . . . He had on no occasion said that cavities could be, or had been injected; he had only suggested the enquiry "what should hinder this operation under favorable circumstances." Much that Green claimed could be done has been done, and who can say that some time in the future some such procedure may not be possible?

It is to be remembered that at this time the laryngoscope and röntgenograms were unknown, and Green could not demonstrate ocularly the things he claimed to do. Occasionally, however, a case presented itself in which the presence of the probang in the trachea could be demonstrated ocularly. A colleague of Green's, Dr. Carnochan, had under treatment a young man who had attempted suicide by cutting his throat. The wound never perfectly healed and a small, permanent, opening into the trachea remained. Green at the request of Dr. Carnochan passed a sponge-tipped probang into the larynx, through the rima glottidis until it appeared at the opening in the trachea. He did the same thing on a patient who had been operated on for tracheotomy. In still another case, where there was a stricture of the œsophagus at the depth of four inches, he passed a probang down to the stricture and then passed a second probang for the distance of 10 inches into the trachea; still many remained convinced that the passage of a sponge-tipped probang into the larynx and trachea was an anatomical impossibility.

Reference has been made to the fact that a considerable number of the cases in which the committee attempted to pass the probang proved unsuccessful; the reason for the failure is not difficult to find. Dr. Green insisted on educating the throat, but the committee neglected this and "whenever the operation was performed by any of the committee, or by Dr. Taylor (one of the physicians at Bellevue Hospital where the experiments were made), it was done, ordinarily, by thrusting one or more fingers of the left hand into the mouth of the patient, and 'feeling for the epiglottis with the index finger';

retaining the finger in this position, the tube, stiffened by the wire, was passed over its extremity and the opening of the glottis felt for, with the curved end of the instrument. Of course 'direct irritation' was thus communicated to the nerves of the larynx, and a spasm of the glottis produced, with great certainty." The wonder is, not that the committee could not pass the tube, but that they ever succeeded in passing the tube.

Green defended himself vigorously before the academy, but much that he said is contained in the above abstracts. Dr. Willard Parker, chairman of the committee, said, "when he heard the paper read, he looked upon it as reflecting credit upon the author and upon New York surgery. He thought it true, until he investigated it. He would say, however, he thought the author honest, and that he thinks he does what he says he does. But he is deceived. There is no mistake about it." Like many other Americans, now as then, Dr. Parker was unable to judge, as Dr. Shanks had intimated, the merit of an American author and he would wait for an European verdict; "It will soon be settled by their voice."

But the midnight hour was passed and it was "the heated term." The committee rose and reported that they had discussed the subject given to their consideration, and referred it back to the academy. An attempt was made to take a vote of the academy on the subject, but it failed. Finally, on motion of Dr. Beadle, it was laid on the table; and there it still rests.

This seems to have ended, for the time being, the active campaign against Horace Green. It had been a bitter contest and one difficult to understand; in its course he had been compelled to resign from one of the medical societies of New York and just escaped expulsion from the Academy of Medicine (Wright). Green laid himself open to criticism by his faulty pathology; and yet, except in the origin of pulmonary phthisis from follicular pharyngitis, Morell Mackenzie supported him. In spite of the opposition and jealousy of many of the physicians in New York, Green built up a very lucrative practice, and, confining his work to laryngeal affections, became the first specialist in this country to devote himself to diseases of the throat.

I now pass to the vindication of Horace Green and the universal acceptance of the claim, which he was the first to put forward, namely, direct medication can be applied to the mucosa of the larynx, and either bronchus can be entered at will.

Bozzini, in 1807, devised a cumbersome instrument with which he claimed to be able to examine the various canals of the body. He, like Horace Green, was severely criticized, though the instrument seems to have done fair work. Babington, an Englishman, in 1829, used what he called a "Glottoscope" constructed on the same principle as the modern laryngeal mirror. Passing hastily over the succeeding 25 years I mention only by name, Liston, Baumes, Selligie, Ephraim Cutter and Avery, all of whom should be considered in an extended account of the development of the laryngoscope, and come to the year 1855, when Manuel Garcia pub-

lished his "Observations on the Human Voice" in which he describes the laryngeal mirror and its use. He used the sun's rays as the source of illumination. Garcia was called the "Father of Laryngoscopy" and lived to see his paper stimulate others to take up the work and develop the modern instruments which have enabled men, like Brünings, Jackson and others, to accomplish such wonderful results. On the occasion of Garcia's one hundredth birthday, laryngologists from all over the world gathered at London to do him honor. He died in 1906, in his one hundred and second year.

Two other names are to be considered in this connection, Ludwig Türck and Johan Czermak. The professional jealousy between these two was extreme. It must be granted that Türck used the instrument to the best advantage, but Czermak invented the concave head mirror with a perforation in its center. This did more to develop laryngoscopy than any other device and, as Czermak developed, without it laryngoscopy would have been "a dead-born child."

In 1859, Störk described the technique of making laryngeal applications of nitrate of silver with the aid of the laryngoscope, and the contention of Horace Green was conclusively settled without further argument.

In 1863, Louis Elsberg presented before the New York Academy of Medicine the results of his laryngoscopic studies and observations. It was before this body of medical men that Horace Green so persistently and courageously defended his claim that the larynx could be entered. He lacked the ocular demonstration, but the laryngoscope now proved the correctness of his contention. The medical profession of these United States should feel honored that it can claim such men as McDowell, Green, Sims and others who have been pioneers in scientific medicine.

As stated in the early part of this paper, Horace Green died in November of 1866. At the meeting of the New York Academy of Medicine held January 2, 1867, the president, James Anderson, one of the members of the committee appointed by the academy to investigate Horace Green's paper who did not sign either the majority or the minority report, announced the death of Horace Green. After this Dr. E. R. Peaslee gave a brief sketch of Dr. Green, from which I take the following abstracts:

Horace Green was no ordinary man. His death covers a large circle of social and professional friends with gloom and by it this Academy is deprived of one of its most distinguished members. At home and abroad his valuable labors in his special department have been recognized and appreciated, and henceforth his name will be enshrined in American Medical History, and be revered as a large contributor to the advancement of the profession to which his energies were devoted.

As a physician, he was a bold and self-reliant practitioner. His self-reliance was doubtless due to his early education; but he was also compelled to rely mainly on himself, from the fact that he was, I may say, the pioneer in the application of local remedies to the respiratory passages. His work on bronchitis, published 20 years ago was the first systematic work on that subject. The small and fragmentary work of Trousseau and Belloc had preceded it, I think, by about five years. The opposition with which he at first met, required no small degree of boldness and self-reliance to overcome and outlive it.

No motives of mere policy ever actuated Dr. Green in his professional relations. He acted always on a thorough conviction of the truth of what he professed, respecting his peculiar method of treatment. Had he been a politic man he would not have gone to Bellevue Hospital, as he did, to attempt to pass the sponge-probing into the tracheæ of patients who had never before been operated on, without previously doing himself the justice to explain that it is generally necessary to accustom the laryngeal mucous membrane to the contact of the instrument before it would pass through the rima glottidis. For he was fully aware that most of those present did not admit that this operation is ever possible, except by mere accident. But he only thought of the practical importance of the operation he professed frequently to have accomplished, and trusted to his experience against the odds arrayed against him. That experience, however, did not, even under these circumstances, fail him.

As a man, Dr. Green was also kind hearted, generous, and transparently honest; though, by such as could not understand him, he was represented to be a crafty, deceptive, and calculating man. As a citizen, Dr. Green was liberal, high toned, and loyal; and in his family, both as a husband and a father, he was affectionate, indulgent, and considerate, and was beloved as but few men are.

Finally, and best and greatest of all, Dr. Green lived and died a sincere, consistent, and humble Christian. And who of us shall leave a higher or a purer record than he, when we in our turn shall follow him.

The following resolutions were then proposed by Dr. Peaslee and adopted by the academy:

Resolved, That the New York Academy of Medicine proudly claims the late Dr. Horace Green as one of its most distinguished fellows, recognizing him as one of its most useful members, as an accomplished physician, a bold and independent writer, a successful teacher, a courteous gentleman, and an honest man.

Resolved, That with unfeigned grief we regret his loss, as one of our associates, as a member of our noble profession, and as a fellow man; and we hereby tender to the bereaved friends our sincere sympathy and condolence.

Resolved, That these proceedings be entered on the minutes of the Academy, and that a copy be transmitted to the family of the deceased.

In his later years there were times when Horace Green had to defend himself against charges other than those we have been considering, which were wrongfully brought against him; but he successfully overcame them and he stands before us a true pioneer in American medicine.

NOTES

Castleton Medical College was established in 1818, and was known as Castleton Medical Academy until 1821, when its name was changed to the Vermont Academy of Medicine. In 1841, its name was again changed and, until it went out of existence in 1861, it was called Castleton Medical College. It had 350 graduates.

The full title of the book Green published in 1846 is, "A Treatise on Diseases of the Air Passages: comprising an Inquiry into the History, Pathology, Causes, and Treatment of those Affections of the Throat called Bronchitis, Chronic Laryngitis, Clergyman's Sore Throat, etc., etc. By Horace Green. New York and London, 1846." This title is, naturally, too lengthy to be placed on the back of a book of 272 pages; the publisher, therefore, condensed it to "Green on Bronchitis, etc." This may, possibly, have occasioned the severe criticism in the Boston

Medical and Surgical Journal where it is called a "misnomer." If so, then the reviewer was far from impartial in his judgment of the book.

RATIONAL SIGNS OF THE MAJORITY REPORT

PROBANG IN TRACHEA

(1) Suffusion of the face rapidly increasing to turgescence and lividity.

(2) Great anxiety and alarm, not easily pacified.

(3) Eyes wild, staring and overflowing with tears.

(4) Cough violent and spasmodic.

(5) Respiration greatly disturbed; inspiration loud, hoarse, and stridulous; expiration attended with violent cough, like that of laryngeal phthisis; ejection of bronchial mucus through the tube, and finally, free breathing through the tube.

(6) Voice extinguished; a hoarse whisper, interpreted with difficulty.

(7) Retching slight.

PROBANG IN OESOPHAGUS

(1) Suffusion of face slight; subsiding, with cessation of retching and cough.

(2) Little anxiety, easily pacified.

(3) Eyes natural, slight suffusion from tears.

(4) Little or no cough.

(5) Respiration little, if at all, disturbed; occasional puffs of air through the tube.

(6) Voice distinct, often quite natural.

(7) Retching and vomiting a common symptom.

FIGURES FROM THE MAJORITY AND MINORITY REPORT

Trials	MAJORITY		
	Failed	Succeeded	% of failures
71	58	11	81
	Hutchings' tube; large curve		
18	3	8	38
	Hutchings' tube; small curve		
38	35	3	92
	Sponge probang		
18	18		100

MINORITY

Dr. Barker accepts, for this occasion only, the figures of the majority. He quotes from the secretary's report giving the number of each individual case.

Failed
9

Doubtful
4

Successful
9

These 22 patients were experimented on with the tube. Dr. Barker comments on the surroundings and physical and mental condition of the patients.

LITERATURE CITED

1839. Trousseau and Belloc: A practical treatise on laryngeal phthisis, chronic laryngitis, and diseases of the voice. Philadelphia.

1846. Green, Horace: A treatise on diseases of the air passages. New York.

1847. Boston Medical and Surgical Journal, Vol. XXXV.

1847. New York Journal of Medicine, Vol. VIII.

1848. Green, Horace: Observations on the pathology of croup: with remarks on its treatment by topical medications. New York.

1850. Boston Medical and Surgical Journal, Vol. XLII.

1853. Erichsen, John: The Science and Art of Surgery. London.

1854. Green, Horace: On the employment of injections into the bronchial tubes, and into tubercular cavities of the lungs. American Medical Monthly, Vol. III.

1855. Reports of the special committee to which the paper of Dr. Horace Green, on "Injections into the bronchial tubes, and into tubercular cavities of the lungs," was referred. Majority and minority report. Transactions of the New York Academy of Medicine, Vol. I.

1855. Discussion on the reports of the committee of the New York Academy of Medicine, to whom was referred the paper of Dr. Horace Green "On the employment of injections into the bronchial tubes and tubercular cavities of the lungs." American Medical Monthly, Vol. III.

1867. Remarks and resolutions on the death of Horace Green. Bulletin of the New York Academy of Medicine, Vol. III.

1914. Wright, Jonathan: A history of laryngology and rhinology. Philadelphia.

THE CORRELATION OF X-RAY FINDINGS AND PHYSICAL SIGNS IN THE CHEST IN UNCOMPLICATED EPIDEMIC INFLUENZA

By ARTHUR L. BLOOMFIELD and CHARLES A. WATERS

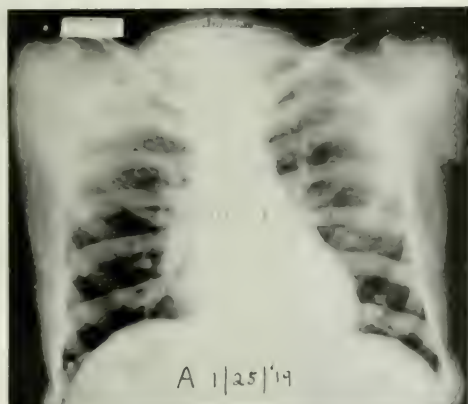
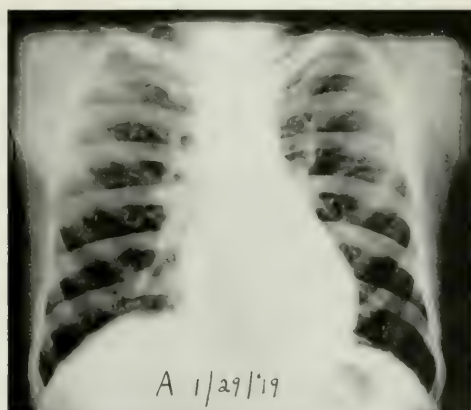
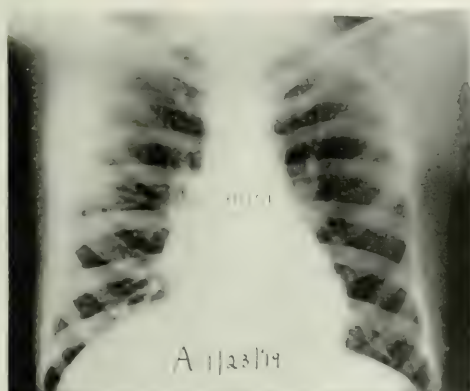
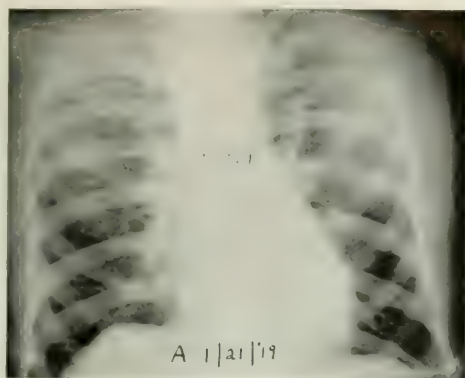
(From the Medical Clinic and the X-Ray Department of The Johns Hopkins Hospital)

The exact significance of the pulmonary lesions associated with epidemic influenza is still a disputed question. In a recent report¹ the view was expressed that bronchopneumonia, although occurring frequently along with or following influenza, was not an essential feature of the disease, but a complication. This opinion was based on the study of an epidemic of severe cases most of which ran their course without demonstrable pulmonary involvement. It seemed possible, however, that small areas of pneumonia might exist even without cough, sputum, or physical signs, especially in the cases in which fever persisted for more than three or four days. The present study

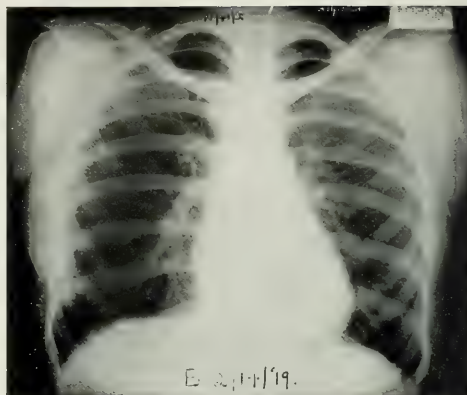
was undertaken to see what light roentgenographic examinations would throw on this question.

The material consisted of 16 consecutive cases of uncomplicated epidemic influenza treated in the wards of The Johns Hopkins Hospital during January and February, 1919. The diagnosis was based on the symptoms, the hyperemic phenomena of skin and mucous membranes, the course of the disease, the duration of the fever, and the presence of leucopenia. In no case was there any evidence of pulmonary complications—the lungs remained clear throughout on physical examination, and cough, if present, was dry and productive only of the usual slight mucoid expectoration associated with the hyperemia of the mucosa of the upper respiratory tract.

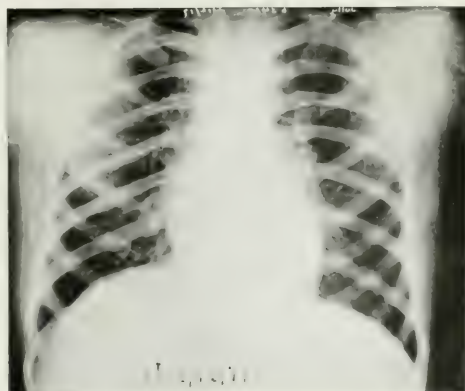
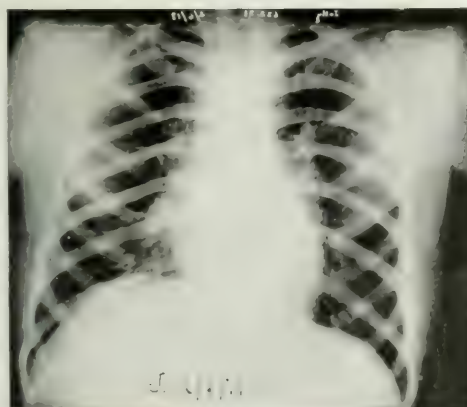
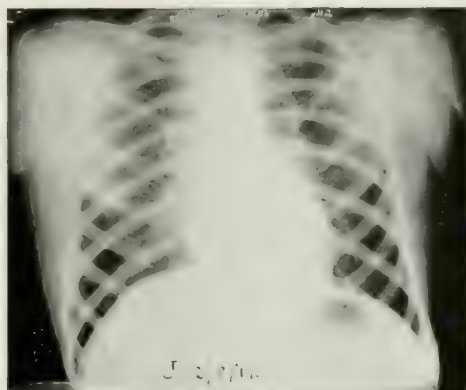
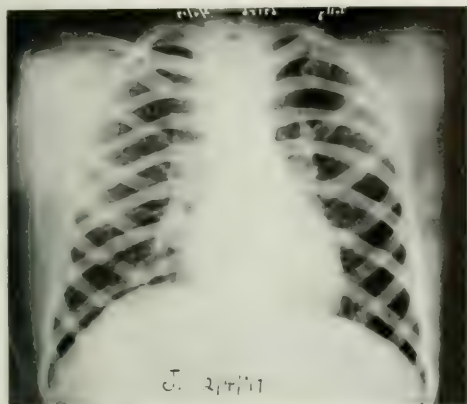
¹ Bloomfield A. L. and Harrop, G. A., Jr.: Bull. J. H. H., 1919, XXX, 1.



SERIES OF PLATES FROM CASE A.



SERIES OF PLATES FROM CASE B.



SERIES OF PLATES FROM CASE J

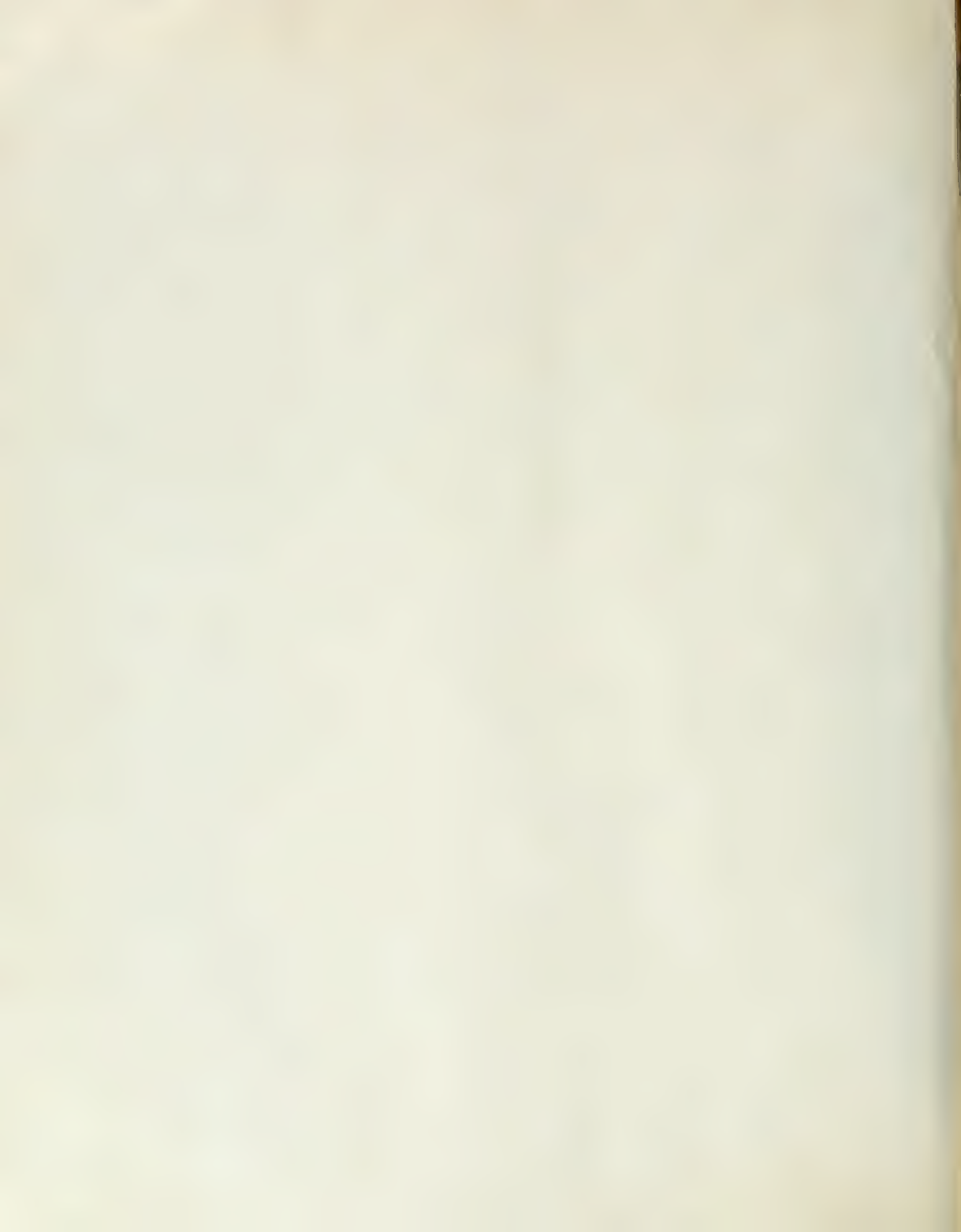


TABLE I

COMPARISON OF CLINICAL AND ROENTGENOGRAPHIC EXAMINATION OF THE CHEST IN UNCOMPLICATED CASES OF EPIDEMIC INFLUENZA

Name	Date of examination	Day of disease	Temperature F°	Physical signs	Cough	Sputum	Day on which temperature became normal	Roentgenograms
V. A.	January 22	4	104°	Normal	Slight, dry	0	5	No signs of consolidation. Well marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 24	6	Normal	"	"	0		"
	" 27	9	"	"	0	0		"
	" 30	11	"	"	0	0		"
M. A.	January 22	4	102°	Normal	Slight, dry	Slight, mucoid	8	No signs of consolidation. Well marked root shadows on both sides. Apices clear. Bases clear. Calcified glands (?) at root of right lung. Pulmonary field shadows remain unchanged.
	" 24	6	101°	"	"	"		"
	" 27	9	Normal	"	0	0		"
	" 29	11	"	"	0	0		"
A.	January 21	4	104°	Normal	Slight, dry	0	9	No signs of consolidation. Marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 23	6	103°	"	"	0		"
	" 25	8	102°	"	"	0		"
	" 27	10	Normal	"	"	0		"
	" 29	12	"	"	0	0		"
	February 1	15	"	"	0	0		"
W.	February 11	4	104°	Normal	Slight	Slight, mucoid	6	No signs of consolidation. Very marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 12	5	100°	"	"	"		"
	" 14	7	Normal	"	0	0		"
	" 17	10	"	"	0	0		"
	" 20	13	"	"	0	0		"
N. B.	February 10	4	101°	Normal	Slight	Slight, mucoid	9	No signs of consolidation. Marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 12	6	100°	"	"	"		"
	" 14	9	100°	"	"	"		"
	" 17	12	Normal	"	"	"		"
	" 20	15	"	"	0	0		"
S. C.	February 11	3	101°	Normal	Slight, dry	0	6	No signs of consolidation. Marked root shadows on both sides. Slight clouding of right apex. Bases clear. Pulmonary field shadows remain unchanged.
	" 13	5	101°	"	"	0		"
	" 17	9	Normal	"	0	0		"
	" 20	12	"	"	0	0		"
D.	February 5	8	102°	Normal	Slight, dry	0	9	No signs of consolidation. Very marked root shadows on both sides. Calcified glands (?) in left root. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 7	10	Normal	"	"	0		"
	" 10	13	"	"	"	0		"
	" 12	15	"	"	0	0		"
J.	February 4	4	101°	Normal	Slight	Moderate mucopurulent	8	No signs of consolidation. Marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 6	6	103°	"	"	"		"
	" 8	8	Normal	"	"	"		"
	" 12	12	"	"	0	0		"
C.	February 11	4	102°	Normal	Slight, dry	0	8	No signs of consolidation. Very marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 13	6	101°	"	"	0		"
	" 15	8	Normal	"	0	0		"
	" 17	10	"	"	0	0		"
S.	February 15	4	102°	Normal	0	0	5	No signs of consolidation. Very marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 18	7	Normal	"	0	0		"
	" 24	13	"	"	0	0		"
F. B.	February 12	6	100°	Normal	0	0	6	No signs of consolidation. Marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 14	8	Normal	"	0	0		"
	" 17	11	"	"	0	0		"
W. I.	February 10	3	100°	Normal	0	0	4	No signs of consolidation. Marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 12	5	Normal	"	0	0		"
	" 14	7	"	"	0	0		"
M. I.	February 8	4	101°	Normal	0	0	5	No signs of consolidation. Moderately marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 10	6	Normal	"	0	0		"
	" 12	8	"	"	0	0		"
G.	January 25	4	102°	Normal	Slight	0	5	No signs of consolidation. Moderately marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 27	6	Normal	"	"	0		"
	" 29	8	"	"	0	0		"
P.	February 1	4	100°	Normal	0	0	4	No signs of consolidation. Well marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 3	6	Normal	"	0	0		"
	" 5	8	"	"	0	0		"
W. A.	February 1	4	102°	Normal	0	0	6	No signs of consolidation. Well marked root shadows on both sides. Apices clear. Bases clear. Pulmonary field shadows remain unchanged.
	" 3	6	Normal	"	0	0		"
	" 5	8	"	"	0	0		"

Roentgenographic examination of the chest was made as soon as possible after admission and thereafter at two- or three-day intervals until the patient was discharged. Each series of plates was studied with two points in mind—first to discover and interpret any abnormal markings, and secondly, to determine any variations in the pulmonary shadows during the course of the disease.

RESULTS

The results of the examinations are summarized in Table I. In no case was there any detectable change in the appearance of the lung markings in a series of from three to six plates made at various times during the febrile and post-febrile convalescent stages of the disease. It would seem, therefore, that the markings were permanent or at least unassociated with

the immediate acute disease. In no case was any shadow seen which could be interpreted as indicating a solidification of the lung. The usual grades of root shadows, in some cases small areas of probable calcification (glands ?) resulting from infections prior to the influenza, and in others slight degrees of apical clouding were seen. It is not the present purpose to discuss the exact significance of pulmonary shadows in general.

CONCLUSIONS

1. Repeated roentgenographic examinations of the lungs during the course of clinically uncomplicated cases of epidemic influenza showed only permanent lung markings.

2. These findings support the clinical impression that bronchopneumonia is a complication and not an essential feature of the disease.

DR. GEORGE PEIRCE

By J. H. MASON KNOX, JR.

On February 4, 1919, Dr. George Peirce, associate chemist of the manufacturing firm of Colgate and Company, Jersey City, New Jersey, died as the result of extensive burns received following an explosion of ether vapor.

The details of the accident could not be accurately ascertained. It is known, however, to have been due to an electric spark discharged in a room in which the Grignard reaction, in which ether is employed, was being carried on.

Following the initial explosion, Dr. Peirce escaped from the building, but re-entered the burning laboratory thinking probably to put out the fire, which was endangering the lives of those in the building, or to save some apparatus. Shortly afterwards he was seen running out with his clothes all ablaze.

Help was near at hand, but before the fire could be extinguished he had suffered severe burns over a large portion of his body and died within a few hours after his removal to the hospital.

The life of Dr. Peirce was one of peculiar simplicity and charm. In the most unostentatious manner he became engrossed in studies in higher organic chemistry to which his inclination and ability seemed to direct him. Dr. Peirce was born in Bristol, Pennsylvania, May 7, 1883. He was the son of Harold Peirce and Charlotte Converse Peirce, now living at Haverford, Pa. From his parents he inherited a devotion to high ideals and a kindly tolerance which were conspicuous qualities in his character. He was the oldest of five children and grew up in the stimulating atmosphere of a home of culture and one given to hospitality.

He prepared for college at the Germantown Academy and graduated at Haverford College with the class of 1903. Here he was holder of the corporation scholarship and a member of the Phi Beta Kappa Society. He immediately entered The Johns Hopkins Medical School and received the degree of M. D. in 1907. In both college and medical school his course was marked by strict application to his duties. He had time, however, to form a number of warm friendships with men of

studious habits who found in Peirce a man who took a real and unselfish interest in their plans.

My own boyhood associations with his father were repeated in the son, as he came regularly to my home to dine each Sunday. On these occasions and on the walks which frequently followed, his absorbing interest in his work, his singleness of purpose and his generous judgment of others were outstanding characteristics.

The originality of his thinking was early evinced. He published later a short paper read before the American Mathematical Society, while still an undergraduate at Haverford, and while in the medical school, in association with Dr. Loevenhart, he carried out a valuable research on lipase.*

After his graduation in medicine he had charge of St. Anthony's Hospital, Newfoundland, organized by Dr. Grenfell.

Later he obtained an internship in the Pennsylvania Hospital, Philadelphia, where he remained for two years as resident physician.

In 1910 he married Miss Ethel Girdwood, of West Orange, New Jersey, who had also been a student of The Johns Hopkins Medical School. In his wife Dr. Peirce found a devoted and sympathetic helpmate who encouraged him in all his subsequent work. Together they went to Germany where Dr. Peirce continued his chemical studies at the University of Berlin, working under the direction of Emil Fischer and other well-known chemists, while Mrs. Peirce served as voluntary assistant at the Kinderklinik of the celebrated Dr. Hübner. After two years he received the degree of Ph. D. in the university, having presented a thesis on "The Alkaloids of the Brucin Group."

Returning to America he accepted an appointment in the University of Wisconsin as assistant in physiology. The following year he was made instructor in pharmacology. Besides his teaching duties Dr. Peirce carried out researches on the ferments and some of the higher monosaccharides.

In 1914 he returned to The Johns Hopkins Medical School as instructor in urology, in charge of the chemical laboratory of the James Buchanan Brady Urological Institute, just completed. He organized and equipped the laboratory and conducted studies on the excretion of sugar by the kidneys.

Two years later, in 1916, he was asked to join the chemical department of Colgate and Company. There he was largely occupied in organic chemical research work in the terpene field and in related work. His associates in the laboratory testify to his "wide thorough knowledge of chemical subjects and of his ability to obtain the practical results he started after."

It was during the prosecution of his investigations that the accident occurred which resulted in his death.

This brief and incomplete sketch can convey only an inadequate idea of Dr. Peirce as he was known to his intimate friends.

He was exceptionally happy in his home life. In Mrs. Peirce he had a companion who because of her training was able to appreciate and further his scholarly ambitions. Three boys with their mother survive him. In this congenial atmosphere Dr. Peirce led the quiet, reserved career of a student. He was loyal to his friends and keenly interested in the march of events about him, but he found his greatest satisfaction in the chemical studies to which he had devoted his life.

In this department of science he had already made important contributions and seemed just at the threshold of his greatest power when he met his untimely end.

He will long be respected and remembered by those who knew him.

Dr. Peirce's published works are as follows:

- "A Curious Approximate Construction for π ." *Bull. Am. Math. Soc.*, 2d Ser., 1901, VII, 426-427.
- "The Inhibiting Effect of Sodium Fluoride on the Action of Lipase." *Jour. Biol. Chem.*, 1907, II, 397.
- "The Deviation of Ferment Action from the Monomolecular Law with Especial Reference to the Esterases." *Jour. Am. Chem. Soc.*, 1910, XXXII, 1517.
- "Ueber den Abbau des Brucins zu einer neuen Base Curbin und einige andere Versuche in der Brucinreihe." *Inaug. Diss.*, Berlin, November, 1912.
- "The Compound Formed Between Esterase and Sodium Fluoride." *Jour. Biol. Chem.*, 1913, XVI, 5.
- "The Partial Purification of the Esterase in Pig's Liver." *Jour. Biol. Chem.*, 1913, XVI, 1.
- "The Excretion of Sugar by the Kidney." *Proc. Soc. Exp. Biol. & Med.*, May, 1915, XII.
- "The Configuration of Some of the Higher Monosaccharides." *Jour. Biol. Chem.*, 1915, XXIII, 327.

ESTIMATE OF SOME OF DR. PEIRCE'S PAPERS

By PROFESSOR E. EMMETT REID, The Johns Hopkins University

Dissertation: "Ueber den Abbau des Brucins zu einer neuen Base Curbin und einige andere Versuche in der Brucinreihe." Berlin, 1912. (On the degradation of brucine to a new base, curbin, and some other experiments in the brucin series). A

skillful piece of experimental work on a difficult and important problem. Although the end of the problem was not reached, a number of steps were taken towards the final solution and, so far as he went, clear and definite results were obtained.

"The deviation of ferment action from the monomolecular law with especial reference to the esterases" (*J. Am. Chem. Soc.*, 1910, XXXII, 1517). A careful study of the rate of hydrolysis by lipase prepared from pig's liver. The velocity is found not to agree with the mass law if the reaction is considered a monomolecular one, in the ordinary sense, but it is shown that by regarding it as a two-stage reaction and assuming that the enzyme and ester form an intermediate compound the results obtained can be harmonized with the mass law.

"The inhibiting effect of sodium fluoride on the action of lipase" (*J. Biol. Chem.*, 1907, II, 397). A large number of quantitative observations are made on the velocity of hydrolysis of a number of esters by lipase in the presence of varying amounts of sodium fluoride which is found to retard the reaction enormously. The amount of such retardation is found to vary greatly with the ester studied. Other salts were tried for comparison. A large number of interesting facts are brought out, the explanation of which will be found in a subsequent paper.

"The compound formed between esterase and sodium fluoride" (*J. Biol. Chem.*, 1913, XVI, 5). This paper is in effect a continuation of the one preceding, explaining the inhibiting effect of sodium fluoride by assuming that the sodium fluoride combines with the enzyme to form a compound that is no longer active. A large number of quantitative experiments are given, the results of which will agree well with this assumption.

"The configuration of the higher monosaccharides" (*J. Biol. Chem.*, 1915, XXIII, 327). The configuration of galactose, mannose and mannose are obtained. The paper shows a good working knowledge of the reactions in the sugar group and a number of difficult preparations were made. The results obtained fill in gaps in our knowledge of the sugars.

APPRECIATION OF THE MAN AND HIS WORK

By PROF. JOHN J. ABEL, The Johns Hopkins Medical School

In 1905 George Peirce spent part of a year in my laboratory engaged in a research under the direction of Dr. A. S. Loewenhardt (The Inhibiting Effect of Sodium Fluoride on the Action of Lipase, *Jour. Biol. Chem.*, XI, 5). It was then that I learned to know him and through numerous conversations with him I soon became convinced that he was a young man of great ability and of high promise for the future. His method of attacking a problem was that of an open-minded investigator and he early showed the capacity to seize upon the salient points of a problem and to separate them from their entangling alliances with troublesome non-essentials. His clear-sighted vision is well illustrated by the manner in which he rounded out his knowledge. After graduating from The Johns Hopkins Medical School, and serving as an interne and house officer in the Pennsylvania Hospital in Philadelphia, he saw that

he could not accomplish his purpose as an investigator unless he acquired a better theoretical and working knowledge of organic chemistry.

It is a pleasure to recall that I had the honor to be consulted by him at this critical step of his career. As the result of mature deliberation on his part and with the hearty sympathy of a wise father, Peirce decided to enter upon a thorough course in chemistry under the direction of Emil Fischer, Professor Leuchs and other leaders of chemical thought in the University of Berlin. This part of his career has already been referred to by Dr. Knox, and I speak of it here because I know that his years abroad were of the greatest intellectual value. He was, of course, well prepared to take up advanced work. His dissertation on brucin and his paper on the configuration of the higher monosaccharides give proof that he rapidly mastered the methods of organic chemistry.

His paper in collaboration with Norman M. Keith, on the excretion of sugars by the kidney, published in the Proceedings of the Society for Experimental Biology and Medicine, VIII, No. 8, appears to me to be his best piece of work. Here an entirely new hypothesis is offered in explanation of the excretion of sugars by the kidney. Many hypotheses have been advanced to account for the fact that normally only the minutest trace of sugar is present in the urine, whereas, if the blood sugar rises beyond a certain level, some will appear. However, none of these hypotheses have been generally accepted. Peirce believed that the true explanation is this: Sugar normally gains entrance into the kidney cells in proportion to its concentration in the blood. During its passage through the cell, some of it is oxidized and if not too much has entered the cell all of it will be oxidized and none appear in the urine. In testing out his hypothesis he made use of published figures for the concentration of various substances in the blood and

urine and made some experiments of his own. He says, "We have found that very roughly speaking a dog of 10 k. body weight with a blood sugar content of 0.1 per cent should excrete about 0.7 gm. sugar per hour if the kidney were completely permeable and secreting freely. During marked diuresis Barcroft and Brodie found that about 660 c. c. of oxygen would be required by the dog's kidneys for the same period. 0.7 gm. of sugar requires 520 c. c. of oxygen for complete oxidation to CO₂ and water. The correspondence is fairly close."

He also estimated that the sugar content of the renal vein should be about 80-90 per cent of the sugar content of the renal artery if the kidney is completely permeable. As a matter of fact Peirce and Keith found by analyzing simultaneous samples of the blood from the femoral artery and renal vein, in five experiments, a difference of 10 to 15 per cent, in three experiments, no difference, and in two, a slightly higher content in the renal vein than in the artery. His studies led him to conclude that only the sugars that are oxidized by the body will show the so-called threshold phenomenon, and he feels justified in making the general statement: If the kidney is permeable for a sugar, when and only when its concentration in the blood rises beyond a certain level, that sugar is oxidized by the kidney. In a foot-note, he even ventures to suggest on purely theoretical grounds the following: If the kidney is permeable for any substance, when and only when its concentration in the blood rises beyond a certain level, that substance is metabolized by the kidney.

Had this young man of high promise been spared he would no doubt have carried out extensive researches in support of this novel hypothesis, and in time, when properly supported by experimental data, we may hope that it might have become known as Peirce's law.

BOOKS RECEIVED

Interstate Commerce Commission. Thirty-second Annual Report of the Interstate Commerce Commission. December 1, 1918. 8°. 192 pages. Government Printing Office, Washington.

The Medical Association of the Isthmian Canal Zone. Proceedings, January, 1917, to June, 1917. Vol. X, part I. Published by the Health Department, the Panama Canal. 1918. 8°. 149 pages. Panama Canal Press, Mount Hope, C. Z.

Surgical Treatment. A Practical Treatise on the Therapy of Surgical Disease for the Use of Practitioners and Students of Surgery. By James Peter Warbasse, M.D. In three volumes with 2400 illustrations. Volume I, 947 pages; volume II, 829 pages. 1918. 8°. W. B. Saunders Company, Philadelphia and London.

Paper Work of the Medical Department of the United States Army. A Guide for Administrative Work. By Ralph W. Webster, M.D., Ph.D. Approved for publication by direction of the Surgeon General of the U. S. Army. 1918. 8°. 541 pages. P. Blakiston's Son & Co., Philadelphia.

Hygiene in Mexico. A Study of Sanitary and Educational Problems. By Alberto J. Pani, C. E. Translated by Ernest L. de Gogorza. 1917. 12°. 206 pages. G. P. Putnam's Sons, New York and London.

Saint Thomas's Hospital Reports. New Series, Vol. XLIV, 1915. Edited by Dr. J. J. Perkins and Sir Charles A. Ballance, K. C. M. G., C. B., M. V. O. 1918. 8°. 141 pages. J. & A. Churchill, London.

The Humane Society of the Commonwealth of Massachusetts. An Historical Review, 1785-1916. By M. A. DeWolfe Howe. With illustrations. 1918. 8°. 398 pages. Printed for the Humane Society at The Riverside Press. Cambridge, Boston.

Library of Congress. Report of the Librarian of Congress and Report of the Superintendent of the Library Building and Grounds. For the Fiscal Year Ending June 30, 1918. 8°. 191 pages. Government Printing Office, Washington.

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INSUSCEPTIBILITY OF MAN TO INOCULATION WITH BLOOD FROM MEASLES PATIENTS

By ANDREW WATSON SELLARDS, Major, M. C., U. S. A.

(From Base Hospitals, Camp Devens, Mass., and Camp Meade, Md.)

INTRODUCTION

In congested communities the sanitarian experiences greater difficulty in the control of diseases of the respiratory tract than in the case of those infections in which the portal of entry is by way of the alimentary canal. From the standpoint of epidemiology, measles should certainly be classified with the respiratory diseases; it takes a prominent place among the most highly communicable infections, being excelled, perhaps, only by pneumonic plague. In the mobilization of recruits even the uncomplicated cases of measles may produce a high non-effective rate; in addition to this disadvantage the serious pulmonary complications of the disease render desirable the development of a protective immunization against the primary infection. Investigations for this purpose would require the inoculation of human subjects on a basis which is necessarily more or less experimental in character. Indeed, of the serious infections of man, the virus of measles like that of scarlet fever and yellow fever* can be definitely identified only by the inoculation of susceptible human individuals. During the recent military emergency, a need and an opportunity arose for the investigation of measles such as would not occur in civil life. Accordingly, Colonel Frederick F. Russell recommended to General William C. Gorgas and to General Meritt W. Ireland the study in human volunteers of the ques-

tion of prophylactic inoculation against measles. In time of need the individual soldier was found ready and willing to offer his services and to accept such risk as was inherent in these inoculations. A precedent for this type of work has been firmly established; the conditions in army life seem especially favorable for the development of preventive medicine as evidenced by the progress in the control of yellow fever, of typhoid and of trench fever.

LITERATURE

Human Inoculations.—Accurate records of the experimental production of measles in man are meager in the extreme. The easy recognition of the disease by its clinical symptoms would seem to render of interest the investigations conducted before the bacteriologic era. For example, Mayr² in 1852 reported the occurrence of measles after an incubation period of two weeks in two of three subjects inoculated on the nasal mucous membrane with nasal secretions of a patient. In another experiment, Mayr reports that mild but typical attacks were produced in each of six subjects by introducing into the skin the scrapings from a morbillous lesion. The incubation period is not stated; no mention is made of any precautions to avoid spontaneous infection.

Recently Herrman³ (1915) inoculated 40 infants under five months of age on the nasal mucous membrane with nasal secretions from cases of measles. This was done, not with the

* In a recent communication Noguchi reports the discovery of the etiologic agent of yellow fever.¹

idea of producing the disease but with the expectation of establishing an immunity, taking advantage of the relatively high insusceptibility of infants to measles in the first few months of life. None of these 40 infants developed any definite symptoms. About 1 to 2 years later, 4 of these children came in intimate contact with measles cases and two were reinoculated without developing the disease.

The first experimental inoculations of blood were performed by Hektoen⁴ in 1905; this observer conducted two independent tests and reported an attack of measles in each instance. Blood for inoculation was taken during the eruptive stage and was incubated before injection, for one day at 37° C. in ascitic broth (1 part ascitic fluid to 2 parts meat infusion broth). In one patient the specimen of blood was withdrawn 6 hours and in the other 30 hours after the eruption had appeared. Moderate quantities (3 c. c. and 2.5 c. c.) were inoculated into flasks of ascitic broth (50 and 75 c. c. amounts). After incubation for 24 hours, this mixture was apparently sterile; there was no evidence of secondary contamination or of any multiplication of the virus of measles as indicated by the gross appearance, by microscopical examination and by the subsequent results of sub-inoculation on a variety of media. Accordingly subcutaneous injections were made (4 and 5 c. c.) into two volunteers and apparently a mild but typical attack of measles developed in each case after an incubation period of about two weeks. This volume of broth culture represents a calculated quantity of blood serum of approximately 0.1 c. c. All viruses known to multiply in culture media produce either macroscopic or microscopic evidence of their growth; both manifestations appear in the vast majority of cases. It would seem from these results, therefore, that a very small amount of measles blood is infective and that it retains its virulence for at least a day *in vitro* at incubator temperature. Such a conclusion is of far-reaching importance. In the investigation of a disease of unknown etiology a great advantage is achieved by the isolation of its virus in a relatively concentrated form uncontaminated by other micro-organisms; one is then in possession of suitable material for the investigation of fundamental features such as immunization of the natural host, transmission to other species and studies in morphology and cultivation. Practically the entire superstructure of modern experimental work in measles rests on these two experimental cases. One may call attention more especially to the reported transmission of the disease to monkeys by inoculations of blood and the isolation of a micrococcus from the blood stream by Tunnichliff.⁵

Inoculation of Monkeys.—Of the recent investigators, Anderson and Goldberger⁶ were the first to report the successful inoculation of monkeys with measles. Two of their conclusions are of especial interest in connection with the data reported in this paper, namely: (1) that the blood of early cases is infective and (2) that the virus of the disease as it occurs in the blood is capable of passing a Berkefeld filter.

DESCRIPTION OF EXPERIMENTAL WORK

In arranging the preliminary protocol of the following work, the reported transmission of measles by the inoculation of blood was accepted as a basis for the first series of injections, arrangements being made to conduct a control for confirming the findings concerning the infectivity of the blood. In order to provide a secure foundation for the more elaborate and time-consuming experiments it was expected in the course of these investigations to obtain information concerning the constancy with which the blood of individual cases is infective, the minimal quantity which suffices to produce the disease and also the extreme limits during which the virus may be demonstrated in the blood. Inasmuch as a very favorable control for the first series of inoculations failed, the question of the infectivity of the blood in measles was accepted as the primary problem; the ultimate object of these investigations consists in determining whether a method of active immunization can be developed, without producing a serious reaction. Injections of blood from patients in various stages of the disease have been made into supposedly susceptible individuals but no symptoms of measles appeared in any instance. Two individuals who had been injected with blood were subsequently inoculated on the mucous membrane of the upper respiratory tract with nasal secretions of an early case of measles but no symptoms developed. There is some reason to believe that these individuals were protected by the preliminary injection of blood.

Arrangements and Preparations for Inoculations.—These investigations were conducted at Camp Devens, Mass., and at Camp Meade, Md. Camp Devens covers an area of approximately 16½ square miles with a normal capacity for 35,000 to 45,000 troops. The Base Hospital is situated at the extreme end of the cantonment opposite the principal entrance to the reservation. The wards of the hospital itself together with the essential accessory buildings such as the quarters and barracks for officers, nurses, and enlisted personnel, as well as the drill and recreation field, occupy an area of approximately 2½ square miles; this section is separated from the nearest barracks for troops of the line by a distance of about ½ mile. The normal capacity of the hospital is 2000 patients which in a time of emergency has been trebled. At the time of these investigations approximately 1000 troops of the enlisted personnel were assigned to the base hospital. Volunteers were obtained largely from this group of enlisted men since the majority of the medical officers had already been exposed to measles; a considerable proportion of these men had not come in contact with patients, being assigned to duty in the barracks and quarters, in the offices and on fatigue work out of doors. Conditions at Camp Meade were fundamentally identical with those at Camp Devens. The work was transferred to Camp Meade, partly for the purpose of obtaining volunteers from the more isolated rural communities, the majority of the volunteers at Camp Devens having come from the smaller towns.

Precautions Concerning Volunteers.—In the acceptance of volunteers for inoculation with measles there are two cardinal

factors which outweigh all other considerations, namely: (1) the general health of the individual with special consideration of the respiratory tract and (2) the assurance that the adult in question has never had a recognizable attack of measles.

Under ordinary circumstances the virus of measles *per se* does not produce serious results in normal individuals; its disastrous effects arise from the secondary infections. The most important of these are the pneumonias especially those from the pneumococcus, the tubercle bacillus and the hæmolytic streptococcus as in the winter of 1917-18. In addition to thorough physical examination, special attention was given to the points indicated in the following outline in order to secure the fullest possible protection for the volunteers:

I. Bacteriological cultures of throats (several examinations at intervals of three to four days) for,

1. Hæmolytic streptococcus.
2. Pneumococcus (any type).
3. Meningococcus.
4. Diphtheria bacilli.
5. Pfeiffer bacillus.

II. Precautions against tuberculosis,

1. History.
2. Physical examination.
3. X-ray findings.

III. Anatomical examination of,

1. Tonsils.
2. Sinuses.
3. Middle ear.

IV. Special isolation for acceptable individuals in order to protect them from intercurrent infections and from spontaneous infection with measles.

V. Special nursing by persons of long experience with measles for any individuals contracting the disease.

If a prospective volunteer showed any of the preceding organisms in the cultural examination of the throat and nasopharynx he was at once eliminated from consideration regardless of whether the organism in question subsequently disappeared. A comparatively large proportion of individuals proved to be unsuitable either on account of the presence of the hæmolytic streptococcus or the pneumococcus. Only a few were rejected on account of a suspected latent tuberculosis. The anatomical examination of the tonsils seemed distinctly important. Individuals who had had an infection of the tonsils at all recently were not considered because, especially under these circumstances, cultural examination of the surface of the gland gives little information concerning the flora contained within the tonsillar crypts. In view of the difficulty of rigidly excluding the presence of the hæmolytic streptococcus by bacteriologic examinations it seemed much safer to conduct these inoculations at a time when infections with this micro-organism were not prevalent in camp. As a practical test of the significance of cultural examinations, Levy and Alexander¹ have noted a very low incidence of complications due to the hæmolytic streptococcus in measles cases whose throat cultures were negative for this organism.

Proper isolation possesses a two-fold importance. In the first place it was very necessary that volunteers found free of pathogenic micro-organisms should be protected from accidental contamination, especially by carriers; secondly, it is of course essential to provide against the possibility of spontaneous infection with measles. With these objects in view, the acceptable volunteers were segregated in a ward removed as far as circumstances would permit from the wards reserved for cases of measles, a distance of about $\frac{1}{2}$ mile. Satisfactory isolation over the rather long period of these experiments was rendered comparatively simple by the discipline developed in military life and by the faithful cooperation of the volunteers themselves. The attendants on the ward for the volunteers were restricted from seeing any patients, but they were not required to isolate themselves. By observing the precautions just outlined, it was felt that the possible dangers inherent in these inoculations would be reduced to a minimum.

Probably the greatest difficulty in these investigations consists in the selection of susceptible adults; in the large cities only a very small proportion of individuals, perhaps 5 per cent, come to adult life without having contracted measles. Age *per se* confers no immunity. Moreover, the disease runs a clinical course which is remarkably true to form. Unrecognized attacks such as abortive cases without a rash constitute, if they occur at all, virtually a negligible factor. The chief difficulty arises from the fact that little or no dependence can be placed on the statement of even the educated adult that he has never had measles. Information was obtained according to the following plan: A census of the detachment was taken and those individuals were at once eliminated who reported having had either measles, "German measles," or scarlet fever.† These three diseases were included on account of possible errors in diagnosis. A limited number were sure that they had had none of these infections; the parents of these men were consulted. At Camp Devens this was done, whenever possible, by the individual himself in person; at Camp Meade a letter was sent to the family of the soldier. Inquiry was made in the first place concerning the individual himself, and secondly, whether he had been exposed to measles through its occurrence in other members of the family. After this information was obtained, an opportunity to volunteer was given to the men in whose cases the replies from the parents were satisfactory, provided that the preliminary bacteriologic examination of the individual was negative. The first cultures were made while the history was being obtained; the final examinations were completed only after the individual had volunteered and had been isolated.

The general plan of the inoculations was designed with the purpose of eliciting the desired information concerning the virus of measles with the production, however, of only an absolutely minimal number of cases of the disease. By employing large series of volunteers, the experimental data could have been obtained rapidly on an extensive scale but only at the cost of

¹ A detailed report of this census will appear in *The Military Surgeon*.

increased risk to the individuals. With the passing of the military emergency, less attention was given to the time consumed in these experiments, the primary object being to avoid the possible production of measles in man without obtaining results proportionate to the serious responsibility of human experimentation.

PRELIMINARY INOCULATIONS OF HUMAN SUBJECTS

Selection of Measles Cases.—There are two essential criteria which must be met in the selection of measles cases for sub-inoculation of normal individuals: (1) the patient must be secured in relatively early stages of the disease and (2) he must be free from all other infections, notably syphilis. At the beginning of this work, the collection of blood specimens was purposely delayed until after the rash had appeared; although the blood might, very possibly, be more infective in the pre-eruptive stage, it seemed advisable to duplicate conditions which had previously given positive results in human experimentation.

For the exclusion of syphilis, dependence was placed on a thorough history in all its aspects, clinical examination and the Wassermann test.

Preliminary Inoculations.—The first inoculations were designed to give preliminary information on the following points:

- (1) Whether the serum alone, free from red cells, contains the virus of measles.
- (2) Whether the organism of measles will pass through a Berkefeld filter.
- (3) Whether a series of injections of patient's and convalescent's serum would immunize a human subject without producing an attack of the disease.
- (4) Whether a previous attack of measles confers complete immunity or whether a modified attack might result in a partially immune subject with possible attenuation of the virus.

For these inoculations, blood was taken from a moderately severe case of measles 12 hours after the first appearance of the rash. At this time the Koplik spots had already disappeared, the eruption was profuse over the face, back and chest, less intense over the abdomen and only a few scattered spots had appeared on the thighs.

Immediately after collection, one portion of the blood was defibrinated and another was centrifuged for the collection of serum. Part of this serum was mixed with an equal volume of fresh serum obtained from a typical case of measles 10 days after the temperature had returned to normal. Another portion of the original serum was diluted with nine parts of physiological saline; one portion of the diluted serum was kept at room temperature for a control and the remainder was heavily inoculated with *B. prodigiosus* and passed through a Berkefeld filter (so-called N).‡

This was an old filter, much worn, which on several previous tests had successfully held back *B. prodigiosus*. When immersed

in water, an additional pressure of 50 mm. of mercury was sufficient to force a fine stream of air through this filter. The time employed in filtering 25 c. c. of the diluted serum was 30 minutes and the pressure was 40 to 50 mm. of mercury; the room temperature was 22° C. Twelve cubic centimeters of the filtrate were inoculated in varying amounts on agar plates and into flasks of broth; the culture media subsequently showed no evidence of growth.

The following subcutaneous injections were made into susceptible individuals: For convenience the susceptible men will be designated by a Roman numeral and the immune by a letter. One volunteer (I) received 5 c. c. of diluted serum (1-10) unfiltered and kept at room temperature one hour; another (II) received 10 c. c. of filtered serum (1-10 dilution) one hour after collection of the blood; a third (III) received 0.5 c. c. of a mixture of equal parts of patient's and convalescent's sera (undiluted) after incubation for one hour at 37° C.

An immune (A) who had measles 28 years previously received 7 c. c. of defibrinated patient's blood 1½ hours after collection.

None of these four individuals developed any symptoms of measles. Neither did any local changes appear at the site of injection except in the individual who received 7 c. c. of defibrinated blood; in this subject a day after the injection, moderate tenderness on pressure developed accompanied by slight erythema over the injected area. These symptoms persisted for three days.

The chief interest in these negative results centers in the control individual who was expected to contract measles. The delay of one hour before injecting this serum and also the absence of red cells might be regarded as factors contributing toward the negative result. It would appear from previous work that the blood retains its infectivity *in vitro* for at least a day. As regards the red cells, as far as we know, all diseases caused by parasites of the red corpuscles are transmitted by insects whereas droplet infection constitutes the accepted mode of transmission in measles.

The failure of filtered measles serum to infect an apparently susceptible human subject must be borne in mind in connection with the positive result reported by Goldberger and Anderson* upon the inoculation of monkeys with filtered serum. These investigators conducted four experiments; in the first two, the results were negative; in the third, one of four monkeys presented slight symptoms only; in the fourth experiment one of two monkeys developed an eruption 21 days after inoculation. These authors conclude that the virus of measles is capable of passing through a Berkefeld candle. No details are given concerning the size of the filter employed or the manner in which the filtration was controlled and conducted.

For the mixture of measles serum and convalescent patient's serum, it was originally intended to conduct a long series of injections gradually eliminating the convalescent patient's serum. It was also intended to hyper-immunize by several intravenous injections of measles serum the immune (A) who failed to develop symptoms after receiving a large quantity of blood subcutaneously. After an interval of one month, a second injection was given consisting of 1 c. c. of serum intravenously. This was collected from a patient 15 hours after the appearance of the rash. No symptoms of any kind resulted from this intravenous inoculation. This work was then sus-

‡ The gradations of Berkefeld filters into coarse, medium and fine (V-N-W) was found frequently to bear little relation to their actual porosity.

pending pending confirmation of the existence of the virus of measles in the circulating blood.

INOCULATION OF SUSCEPTIBLE INDIVIDUALS WITH MEASLES BLOOD

Inoculation of De-fibrinated Blood and of Blood Incubated in Ascitic Broth.—The remainder of the work with susceptible individuals has been restricted to an attempt to transmit measles by the injection of patient's blood. Defibrinated blood was injected subcutaneously into two men. Cultures of patient's blood in ascitic broth were inoculated in two other men. This duplication of a method for which successful results have been reported seemed essential in view of the negative result following the inoculation of serum without preliminary incubation. None of these four subjects developed measles; neither did any symptoms appear that could be definitely attributed to the injections. The details are as follows:

Defibrinated blood from an early case of measles, 12 hours after the appearance of the rash, was injected subcutaneously in 2 c. c. quantities in the interscapular area, after a delay of 15 minutes, into two susceptible volunteers. The patient's blood (4 c. c.) without defibrination was added to ascitic broth (50 c. c.) consisting of two parts of meat infusion and 1 part of ascitic fluid. The broth was prepared without the addition of sugar and its reaction to phenolphthalein was equivalent to 1 per cent of normal acid. The ascitic fluid was yellow in color, sp. gr. 1.018 and was free from bile pigments. Repeated aerobic and anaerobic cultures showed no evidence of growth; the ascitic fluid was therefore used without preliminary sterilization. In the culture medium prepared by Hektoen the ascitic fluid was heated at 55° C. for 54 minutes. Differences of an altogether minor nature probably occurred also in the reaction and composition of the broth and ascitic fluid which was employed.

This medium inoculated with the patient's blood showed no evidence of growth after 24 hours' incubation; accordingly, two susceptible men (VI and VII) were inoculated subcutaneously in the interscapular area with 10 c. c. of this mixture of blood in ascitic broth, the mixture being shaken to include corpuscles as well as serum. This quantity represents about 0.2 c. c. of patient's serum.

During the incubation period these men were observed with special reference to:

1. Development of symptoms in the upper respiratory tract.
2. Occurrence of Koplik spots.
3. Body temperature.
4. Total and differential leucocyte count.

A record of the temperature by mouth and of the pulse and respiration was taken as a routine at four-hourly intervals during the day. The entire surface of the body was examined for cutaneous rashes, since, after inoculation, the initial lesions might appear first not necessarily on the face or chest, but on any part of the body. All of these individuals remained essentially free from symptoms.

Inoculation of Skin Lesions.—After an interval of 7 days one of the men injected with defibrinated blood (IV) and another (VII) injected with blood incubated in broth were re-inoculated by smearing the mucous membranes of the eyes, nose and throat with freshly excised morbillous skin lesions. These inoculations possessed a two-fold interest in that a positive result would demonstrate that the virus of the disease is present in the skin lesions and that these individuals who were refractory to an injection of blood were nevertheless sus-

ceptible to the disease. No definite symptoms developed. In view of these negative results, the question arose of testing experimentally the susceptibility of these men by inoculating the upper respiratory tract with secretions from the mucous membranes of active cases. The injections of blood, however, had been made from only one case of measles, a single specimen of blood having been taken. Therefore, if the use of nasal secretions should produce measles in one of these subjects, it would only establish that, in a single case of measles, one specimen of blood at a given stage of the disease did not prove infective for a susceptible host. It seemed desirable to defer tests of susceptibility until individuals could be inoculated with blood from several stages of the disease and preferably from more than one patient.

Inoculation of Blood from Pre-Eruptive and Eruptive Stages.—Accordingly for the next step, two susceptibles were inoculated on two successive days with blood taken before and after the appearance of the eruption. Control inoculations were made simultaneously into two immunes. Blood for these injections was secured from two patients; specimens were obtained from one case 30 hours and again six hours before the appearance of the rash and from the other six hours before and 18 hours after the rash appeared. None of these four subjects developed any symptoms of measles.

Of the two susceptibles selected for these injections, one (IX) gave unusually good evidence that he had never contracted measles. This individual had grown up on a farm in West Virginia and had always lived at home. He was 26 years of age being the sixth of 8 children of whom the youngest was 20 years and the eldest 38 years of age. Information was received from the mother and the eldest sister to the effect that measles had never occurred in the household. Then in adult life several older and younger brothers and sisters left home and contracted measles. Of the five older members of the family, the eldest sister contracted measles in 1910; two brothers, the second and third members of the family, developed measles in March, 1917; the fourth member, a brother, has not had measles; a sister, who was the fifth child, developed measles in 1908. Of the two younger children one, a sister, 20 years of age, has never had measles; the other, a brother, 24 years of age, did not develop measles until he enlisted in the army, having contracted the disease at Camp Shelby, Miss., in December, 1917.

On enlisting this volunteer (IX) was assigned to the medical detachment, working exclusively in the officers' quarters. He entered the hospital only on a single occasion, to visit a friend ill with tonsillitis.

In view of the prevalence of measles in the cantonments it might seem that no susceptible individual could escape infection for any length of time. However, there has been a slight but constant incidence of measles at the ports of debarkation even among the troops returning from overseas, notwithstanding the fact that measles has been widely distributed throughout the training camps of this country.

The two immunes were injected in order to test the protection afforded by an attack of measles and also to control

any minor symptoms that might appear in the susceptibles, such as slight changes in the body temperature and in the leucocyte picture. One of these immunes (A) had already been inoculated with blood on two occasions and with secretions from the mucous membranes of patients; the results were negative. The other immune (B) probably had had measles more than 30 years ago and had not previously received any injections in the course of these experiments.

For these inoculations of blood, very favorable cases of measles were obtained during a small epidemic which developed in a country district outside of the camp. Two adult patients were selected. Blood from each of these cases was mixed with 2 per cent sodium citrate in physiological saline; the two specimens of citrated blood were pooled and the mixture was injected into each subject; 24 hours later a second specimen of blood was collected in the same way from each patient and the injections were repeated. Each subject received injections of blood from two patients at two periods of the disease, *i. e.*, the equivalent of four injections in all. On the first day 10 c. c. of blood were taken from each patient, and mixed with an equal volume of citrate solution. On examination, the first patient showed numerous Koplik spots at this time and six hours later the rash appeared. The temperature was 102.8°. The second patient showed only a few isolated Koplik spots and the rash appeared 30 hours later. The temperature was 99°. These two specimens of citrated blood were mixed; each of the two susceptibles (VIII and IX) and the two immunes (A and B) were then injected with 6 c. c. of the resulting mixture, the injection being given in part subcutaneously and in part intramuscularly in the gluteal region. The maximum period of time elapsing between the withdrawal and the injection of the blood was 45 minutes for the first and 15 minutes for the second patient. A duplicate of these injections was made on the next day, 10 c. c. of blood being taken from each case and mixed with 7 c. c. of 2 per cent citrate solution. At this time the Koplik spots had disappeared in the more advanced case; the rash, which had appeared 18 hours previously, was almost confluent over the face, well developed over the chest and very sparse over the abdomen. In the second patient, the Koplik spots were abundant at this time and the rash appeared six hours later. The temperature was 102.2°. After these specimens of citrated blood had been mixed, the same men (VIII, IX, A and B) were injected with 6 c. c. quantities in the same manner in the gluteal region on the opposite side; the time elapsing between the withdrawal and the injection of the blood for the first case, *i. e.*, the one in which the rash had developed, was 40 minutes and for the second case, 10 minutes. These injections were made subcutaneously and intramuscularly in order to duplicate in the first place the manner of inoculation for which successful results had already been reported. It seemed entirely possible that a virus might find better protection for itself in the subcutaneous tissues than when exposed to the fluids and cells of the blood stream. An intravenous injection in addition to those into the tissues was not made in order to determine whether a rash, if one developed, would appear first at the site of inoculation or on the face as in the spontaneous disease. To facilitate these observations the site of inoculation was changed from the interscapular to the gluteal region.

Some slight local reactions followed these injections. At the site of inoculation one of the two susceptibles (VIII) developed well-marked induration appearing eight days after the first injection, persisting very definitely for four days and gradually disappearing during the next 48 hours. In this individual the induration was bi-lateral; in the other (IX) slight induration without any well-defined margin developed at

the site of the second injection. This also appeared 8 days after the first injection but persisted for only 48 hours. In one of these men (VIII) a very transient erythema appeared for a few hours over the area of induration, on one side only, on the 10th and again on the 11th day after injection. Neither of the two immunes developed any local induration. One of these immunes (A) on being inoculated in a similar manner 5½ months previously developed a local induration entirely analogous to these two susceptibles. The local reaction, therefore, to the first injection of measles blood varied slightly in the two immunes.

SUSCEPTIBILITY TESTS

When it became apparent that no symptoms of measles would develop from these injections of blood, arrangements were made to test the susceptibility of these men by inoculating the mucous membranes of the eyes, nose and throat with the secretions from the mucous membranes of an early case of measles.

A favorable patient was found for these inoculations. A child, five years of age, the daughter of a physician was exposed to measles by the occurrence of an attack in an older sister. During the incubation period in this child, examinations were made of the nose and throat for pathogenic microorganisms, especially the pneumococcus and the hæmolytic streptococcus. None were found and as far as secondary invaders were concerned, the secretions were regarded as satisfactory. Twelve days after exposure the patient developed a moderate conjunctivitis and coryza accompanied by a temperature of 100°. During the next two days, the temperature was practically normal but on the following morning, 15 days after exposure, it rose to 102.5° with a marked increase in the conjunctival and respiratory symptoms. A few Koplik spots were present. On the following morning these symptoms persisted and profuse eruption appeared over the face spreading gradually downward over the body in the course of the next 48 hours.

Inoculations with secretions from the mucous membranes were carried out on the two susceptibles (VIII and IX), on one of the immunes (A) and on another immune (C) who had not previously received any injections. The latter, a man, 23 years of age, had had measles nine years before. Twenty days after the last injection of blood, these four individuals (VIII, IX, A and C) were inoculated on the mucous membranes of the eyes and nose with the lachrymal secretions and also on the nose and throat with the nasal secretions of the patient. This inoculation was performed on the day of the pre-eruptive rise in temperature in the child, *i. e.*, 12 days after exposure and four days before the eruption. A similar inoculation was made on the day before the eruption, *i. e.*, on the 15th day after exposure. On this occasion, in addition to duplicating the previous inoculations, the buccal secretions were thoroughly rubbed over the mucous membranes of the mouth and throat of the four subjects. On both days all of these inoculations were made with a sterile cotton swab slightly moistened with physiological saline. This was rubbed rather firmly over the mucous membrane of the patient and then immediately over the mucous membrane of the subject, a fresh swab being used for each inoculation. On both occasions the

four subjects were in the same room with the patient; on the day of the first inoculations, the patient not being confined to the bed was allowed to play with these men three-quarters of an hour.

Intravenous Injection of Blood.—In addition to these inoculations with secretions of the mucous membranes, one more susceptible (X) was inoculated with measles blood. A specimen was taken from this same child within from 6 to 10 hours after the appearance of the rash; 0.5 c. c. was injected subcutaneously and 1.5 c. c. intravenously immediately after withdrawal before the blood had time to clot.

Neither the intravenous injection of blood nor the inoculations of the secretion produced, in these five subjects, any respiratory symptoms or any rash. Only insignificant fluctuations occurred in the temperature and in the total and differential leucocyte count.

For the susceptibility tests in these men it might naturally be expected that control inoculations would have been conducted with a susceptible individual who had not had any previous inoculations of blood. The production of measles in a control case would furnish some additional evidence but certainly would not in any sense afford proof that these men were susceptible and had been immunized by the injections of measles blood.

In drawing conclusions concerning these inoculations of blood and mucous secretions in these susceptible men, there are two unknown factors to be determined, namely:

- (1) Whether the individuals in question (VIII and IX) at the conclusion of the inoculations were immune and if so
- (2) Whether the immunity was conferred by the injection of blood or acquired possibly through a previous attack of measles.

The results of the susceptibility tests leave little doubt but that these men were immune; they were exposed to natural infection by an early case of measles and they were also thoroughly inoculated artificially. The high degree of communicability characteristic of the disease leaves little room to suppose that these men might be infected by exposure now to a second case. The evidence of susceptibility of one of these volunteers (IX) is certainly much more concrete than the general arguments that can be brought in favor of a previous attack of measles. It would seem distinctly possible that the injection of blood had produced an active immunity.

A priori one would not expect that substantial immunity could be obtained without the production of marked local or general symptoms. However, in the case of variella, Hess and Unger⁸ report active immunization by the intravenous injection of the contents of vesicles without the production of subjective symptoms. It is noteworthy, however, that control individuals inoculated on the mucous membranes failed to develop variella. Recent work by Richardson and Connor,⁹ though affording no final proof, suggests the possibility of obtaining active immunity against measles without the production of definite symptoms.

Lastly it should be emphasized that conclusive demonstration of the non-infectivity of measles blood upon injection into a susceptible individual would still fail to prove the absence of the virus of the disease in the circulating blood. It is very doubtful, for example, whether a susceptible human being would be infected by the injection of a moderate amount of blood of a typhoid patient taken during the stage of bacteremia. It is a theoretical possibility that the blood of a measles patient might reproduce the disease when inoculated on the mucous membranes though not upon injection into the body tissues.

For the sake of convenience, the inoculations reported in the preceding pages have been collected in the following table:

TABLE OF INOCULATIONS

Individual	Material	Amount	Method of Inoculation
Susceptible I.	Blood serum, eruptive stage.	0.5 c.c.	Subcutaneous.
Susceptible II.	Blood serum, eruptive stage, 15 days later.	0.5 c.c.	Subcutaneous.
Susceptible III.	Blood serum, eruptive stage, incubated with convalescent serum.	25 cc.	Subcutaneous.
Immune A.	Debrinated blood, eruptive stage.	7 cc.	Subcutaneous.
1 month later.	Blood serum, eruptive stage.	1 cc.	Intravenous.
2 months after 2d injection.	Mucous secretions, eruptive stage.	On mucous membranes.
2 months after 2d injection.	Citrated blood, pre-eruptive stage.	*3 cc.	Subcutaneous and intramuscular.
1 day after 4th injection.	Citrated blood, pre-eruptive and eruptive stage.	*2 cc.	Subcutaneous and intramuscular.
3 weeks after 4th injection.	Mucous secretions, pre-eruptive stage.	On mucous membranes.
3 weeks after 4th injection.	Mucous secretions, pre-eruptive stage.	On mucous membranes.
Susceptible IV.	Debrinated blood, eruptive stage.	2 cc.	Subcutaneous.
5 weeks later.	Rubellous serum in broth.	On mucous membrane.
Susceptible V.	Debrinated blood, eruptive stage.	2 cc.	Subcutaneous.
Susceptible VI.	Blood, eruptive stage, incubated in broth.	*0.1 cc.	Subcutaneous.
Susceptible VII.	Blood, eruptive stage, incubated in broth.	*0.1 cc.	Subcutaneous.
5 weeks later.	Rubellous skin lesion.	On mucous membrane.
Susceptible VIII.	Citrated blood of two patients, pre-eruptive stage.	*3 cc.	Subcutaneous and intramuscular.
1 day later.	Citrated blood of two patients, pre-eruptive and eruptive stages.	*3 cc.	Subcutaneous and intramuscular.
3 weeks later.	Mucous secretions, pre-eruptive stage.	On mucous membrane.
3 weeks later.	Mucous secretions, pre-eruptive stage.	On mucous membrane.
Susceptible IX.	Duplicate of 4 inoculations of Susceptible VIII.		
Susceptible X.	Whole blood, eruptive stage.	2 cc.	Intravenous and subcutaneous.
Immune B.	Duplicate of the first and second injections of VIII and IX.		
Immune C.	Duplicate of the first and second injections of VIII and IX.		

* Calculated amount.

CONTROL INOCULATIONS

Injection of Ascitic Broth and Normal Blood.—For the intensive inoculation of susceptible individuals with measles blood it might seem only natural to have included the injection of measles blood incubated in ascitic broth in addition to the other injections. A control series of injections, however, had already shown that normal blood in ascitic broth was not altogether free from toxic action.

The same lot of broth and ascitic fluid already described for the incubation of measles blood was mixed with normal human blood

(4 c. c. to 50 c. c. of ascitic broth) and incubated for 24 hours. Quantities of 5 to 7 c. c. were injected subcutaneously into 10 individuals; six remained practically free from symptoms. Of the other four, one immediately after injection maintained a temperature of 99° to 99.5° for nine days; another, six days after injection, developed a temperature of 100.2° accompanied by a few large papules over the forehead and a moderate degree of inflammation of the pharynx; the two others, nine days after injection, developed temperatures of 100° and 101° with definite pharyngeal symptoms but unaccompanied by any rash.

In a second group of controls with the same technique but with another lot of broth and of ascitic fluid, the reactions were similar but rather less marked. Of 10 individuals, three remained entirely without symptoms. The results in the others were as follows: in two cases, 10 days after injection, the maximum temperature in one was 99.8° and in the other 100.2°; three other cases reacted much earlier, the temperature in one on the fifth day being 100° and in the other two 99.4° on the sixth day. One case presented a slight rise in temperature on several days as follows, 99.2° on the fourth and fifth days, 99.4° on the sixth day. On these days, this man also developed a fairly extensive maculopapular eruption appearing first over the chest and then over the arms. When his temperature returned to normal the rash faded leaving pigmented areas which gradually desquamated. Another subject on the third, fourth and fifth days after injection developed a well-marked erythema which was widely distributed over the chest, back, abdomen and extremities. The temperature continued normal, except on the 13th day when it rose to 99.4°. In this second group of controls the leucocytes were counted whenever a rise in temperature occurred, but no leucopenias were observed.

These reactions, though very mild, indicate the advisability of conducting control inoculations when similar injections are performed to test for the presence of a virus; this is especially true in view of the difficulty of duplicating exactly a rather complex culture medium. Although these symptoms did not simulate measles in any way, nevertheless the interpretation of atypical temperature curves or rashes might be confusing; the detection of a pre-eruptive rise in temperature might be very difficult when complicated by the possible effects of ascitic broth.

CLINICAL EVIDENCE

Intra-uterine Infection.—Medical literature, especially the text-books, frequently contain the statement that pregnant mothers, having contracted measles, occasionally give birth to a child with a fully developed rash. These reports of intra-uterine infection do not bear complete evidence of authenticity. In many instances, satisfactory evidence is lacking for the diagnosis of measles especially in the child; in other cases, the period elapsing after birth before the rash appears is sufficiently long to permit of extra-uterine infection. Although the cases are comparatively rare, it appears, on the other hand, that a pregnant mother developing measles at term does not ordinarily infect the child *in utero*. Lastly, the development of measles in a new-born child would not harmonize with the view that infants during the first three months of life are immune from the disease. This apparent discrepancy might be explained by Herrman's⁸ statement that children of susceptible mothers are not immune from measles, a view, however, which is not supported by the natural immunity of infants to some other acute infections, notably scarlet fever and diphtheria.

Characteristics of the Eruption.—The question whether the virus of measles gains access to the circulating blood requires for a completely satisfactory answer the explanation of a striking clinical symptom. *A priori* the remarkably constant appearance of the rash widely spread over the body would seem obviously to point to the distribution of the virus by the blood-stream. Unlike the rashes of other infections, of serum disease and of the food and drug intoxications, the eruption of measles always appears first on the upper part of the body, commonly on the face, from where it spreads steadily downward over the trunk and arms reaching the lower extremities on the second or third day. This phenomenon is very striking and very constant. It has been recognized as one of the distinguishing features of the eruption of measles. The average period for this progress over the body is usually stated as two or three days with extreme limits of one to five days. In a fairly definite but less striking manner the eruption fades in the order of its appearance; thus the rash often almost disappears on the face before it is fully developed on the feet. Virtually no explanation has been suggested for this characteristic progress of the skin eruption. Von Pirquet,⁹ assuming that the virus is present in the blood stream, advances the view that the rash is a manifestation of allergie and that the order of appearance of the skin lesions is directly proportional to their distance from the heart and great vessels. In support of this view, figures are given in detail of the distance from the skin lesions by way of the arteries to the heart. It is very difficult to conceive of any explanation that is consistent with the mechanical features of the circulatory system. Moreover, other exanthems which certainly are distributed by the blood-stream do not progress in this manner over the body. A notable example is small-pox; the portal of entry is probably similar to that of measles, but one commonly examines the palms for the first nodules. Von Pirquet departs widely from the accepted views in considering that the rash of small-pox resembles measles in its origin and progress over the body. Possibly the lymphatic system offers a more satisfactory basis than the circulating blood for the explanation both of the usual point of origin of the rash and its subsequent distribution. The mucous membrane of the upper respiratory tract and of the eyes may safely be regarded as the portal of entry of the virus of measles and the seat of the primary lesion. Notwithstanding some variation in individual cases as well as some minor differences of opinion, the skin lesions usually appear first on the face. It is conceivable that the virus travels by way of the lymphatics not unlike the primary infection of the nasal mucous membrane in leprosy with the subsequent involvement of the skin of the face. The gradual progress of the measles rash has certain features in common with the spread of erysipelas, an infection which travels by way of the lymphatics. The plexus of lymphatics forming a complete network over the body would furnish anatomical communications consistent with the distribution of the rash. The valves of the lymphatic system which normally direct the flow of lymph in certain definite channels would not necessarily constitute an effective barrier against the spread of an infec-

tious agent; a rapidly multiplying virus could conceivably grow against this feeble current of lymph and also grow through the delicate valves.

The preceding discussion has been based on the hypothesis that the morbillous exanthem is produced, not by an extracellular toxin but by the action of the virus of the disease itself, in a manner analogous to what occurs in small-pox and chicken-pox. A toxin could hardly distribute itself either by the blood stream or by the lymphatics in a manner that would explain the symptoms observed in measles. The virus of the disease, if it is distributed by the lymphatics, would almost inevitably be swept into the blood stream where it might readily persist temporarily even though it did not multiply. The clinical evidence, however, can only be regarded as suggestive; experimental proof must be obtained before any final decision is permissible. The ultimate explanation of the progress of the rash of measles will be of distinct interest and value.

DISCUSSION OF RESULTS

There is, unfortunately, a striking discrepancy between the negative results following these inoculations of measles blood and the successful experiments previously reported under essentially similar conditions. A careful examination of the data recorded in this paper has failed to suggest any correlation of these diametrically opposite results. Eight apparently susceptible individuals have been inoculated with blood in various ways but none developed measles. In the selection of measles patients for these inoculations, the diagnosis both of the disease itself, especially during an epidemic, and also the stage of the disease offers little difficulty. In any negative results in adults the crucial factor is the question of susceptibility. While some of these eight individuals may in reality have been immune, it seems that, at the least, several of them must have been susceptible. As already suggested, the two who received intensive inoculations of measles blood and responded negatively to susceptibility tests may have been immunized by the injections; if one is not willing to consider the possibility of immunization there still remain six other cases requiring explanation.

There are certain points of especial interest concerning the two experimental cases reported by Hektoen. The extremely small quantity of serum, approximately 0.1 c. c., employed by this author constituted one of the significant features of his experiment. A few but not many infections can be readily reproduced by the injection of minimal quantities of blood. In cattle plague as little as 1/60 c. c. of blood may prove infective; "Marchoux, Salimbeni and Simond" produced yellow fever with 0.1 c. c. of serum.

It will be recalled that these successful experiments with measles were conducted prior to our knowledge of serum sickness; however, only homologous proteins were employed and typical serum-disease can therefore be eliminated. In the control tests reported in this paper the injection of mixtures of normal blood, ascitic fluid and broth produced a slight temperature and rash in occasional instances, but in no case

could the symptoms have been confused clinically with measles.

Spontaneous Infections.—Sporadic cases of measles may develop so insidiously that even with careful isolation, the possibility of spontaneous infection during experimental inoculations must be borne in mind. A typical illustration occurred at the base hospital at Camp Devens, Mass. A patient had been in the general wards of the hospital for two months; during this period it was not possible to trace any contact with a case of measles. He was then transferred to the psychopathic ward where, after thorough isolation for one month he developed a typical attack of measles. The temperature chart showed a characteristic pre-eruptive rise accompanied by conjunctivitis and coryza. The symptoms increased: Koplik spots appeared, the temperature rose again, a characteristic rash developed followed by the usual pigmentation. It was not possible to locate any third person who might have carried the infection to this patient. Such examples are, however, so rare that it is by no means plausible that both of Hektoen's cases could be explained in this manner. This is especially true in view of the fact that the experimental subjects in question underwent a period of isolation much longer than the normal incubation time of the disease before any injections were made and they were subsequently carefully protected from spontaneous exposure.

The diagnosis of these experimental cases was based essentially on the rise in temperature after a typical period of incubation and the development of a definite rash. In both patients the rash started on the face. In one case the progress of the rash over the body is described; its distribution was almost complete in about five hours. This period would be extremely short for spontaneous measles, being much more characteristic of rubella. Information concerning the lymphatic glands in these patients would have been of some value in differentiating these two diseases. Although the injections were made over the chest and over the back it is of interest to note that the rash appeared first on the face just as when the virus enters the body by way of the mucous membrane. In one of these cases a typical bran-like desquamation is described.

Respiratory symptoms were absent in one of these cases, a feature which has led Ustvedt¹² to suggest the possibility of doubt concerning the diagnosis of measles. However, it is not at all surprising that the mucous membrane of the respiratory tract should escape involvement when one considers that the portal of entry and very possibly the seat of the primary lesion was changed from the mucous membranes to the body tissues. Such absence of respiratory involvement in *measles inoculata* would constitute a hopeful point in securing active immunization without running the risk of pulmonary complications. Likewise, from the standpoint of protective inoculation, it is encouraging to note that evidence of malaise was absent altogether in one patient and very mild in the other.

It is noteworthy that the charts in neither case exhibit any pre-eruptive rise in temperature, a characteristic which though very common is not constant in spontaneous infections and it is certainly not an essential criterion for the diagnosis of

measles inoculata. It is desirable that certain deficiencies concerning these cases should be supplied, more especially the observations concerning the leucocyte count and the occurrence of Koplik spots. This information would be helpful in the differential diagnosis.

In some respects, therefore, these experimental cases differed from the usual course of spontaneous measles notably in the rapidity of the spread of the rash, in the absence of a pre-eruptive rise in temperature, in the absence of respiratory symptoms in one case and of malaise in the other. Such modifications, however, are of an essentially minor nature and might readily be explained as the result of the subcutaneous injection as contrasted with spontaneous infection. The occurrence of such modifications in the disease, however, would require thorough confirmation.

General Considerations.—Some of the infectious diseases of man can be readily transmitted from infected to susceptible individuals by the injection of blood; such transmission has been fully demonstrated for yellow fever,¹² malaria¹⁴ and trench fever.¹⁵ According to the conclusions of Hektoen this same statement would also apply to measles. To appreciate fully its importance, it must be clearly borne in mind that for trench fever, malaria and yellow fever the natural portal of entry is through the skin; in measles the primary lesion occurs in the mucous membrane. By radically altering the portal of entry or the seat of the primary lesion of a given virus remarkable changes may be produced in its effect even on a highly susceptible host; the vibrio of Asiatic cholera produces infection when ingested by way of the alimentary tract but relatively large amounts of living and virulent cultures can be injected subcutaneously with impunity.

After noting certain definite exceptions it would seem possible to develop some general rules concerning fundamental principles involved in the artificial immunization against any given infection. Precise data, from the very nature of the subject, are not available on account of the difficulty of obtaining information concerning the infectivity of pathogenic micro-organisms for man. The subject may be conveniently considered under three headings:

1. *For those infections in which the mucous membrane constitutes the portal of entry and in which the classical lesions of the disease are in general limited to the tissues accessible by direct continuity, the causative organism may in many instances be injected subcutaneously in a viable condition in moderate dosage with impunity.*

In the case of bacillary dysentery and Asiatic cholera, living attenuated cultures of the causative organism have been used freely by subcutaneous injection as a vaccine. For the pneumococcus, Cecil and Blake,[§] at the Army Medical School, have recently demonstrated in monkeys (*Macacus syriacus*) that as little as one-millionth of a cubic centimeter of a broth culture may produce a fatal pneumonia upon intratracheal injection. The subcutaneous injection of one-thousandth of a cubic centimeter of the same culture may or may not produce a

septicæmia. In either case, those animals which recover possess a distinct immunity. In the case of *B. diphtheriæ* virulent strains growing on a wound usually produce no symptoms in man. From the clinical evidence one would not expect that the hypothetical organisms of whooping cough and of influenza would produce an infection upon subcutaneous injection.

2. *As a corollary to the first statement, when the natural portal of entry of a pathogenic organism occurs through the skin, then artificial injection into the tissues or blood stream causes an infection which reproduces the typical manifestation of the spontaneous disease.*

Of the more important diseases in which the portal of entry occurs through the skin we may consider bubonic plague, tetanus, glanders, anthrax, malaria, trypanosomiasis, hydrophobia, kala azar, relapsing fever, typhus fever, yellow fever, dengue fever, trench fever and the spotted fever of the Rocky Mountains. In the case of plague, malaria, yellow fever, trench fever, typhus and probably dengue, it has been demonstrated experimentally that the subcutaneous or intramuscular injection of the virus, in virulent form, reproduces the typical features of the spontaneous diseases; a similar result could be confidently expected in the remainder of the diseases just mentioned.

The disease, plague, occupies a position of an intermediate type which is unique. *B. pestis* exhibits the characteristic of possessing two distinct portals of entry resulting in the production of two clinical types of disease, the pneumonic and the bubonic form of plague. If insect transmission of *B. pestis* were unknown, bubonic plague would not occur spontaneously; experimentally it could be designated appropriately as *plague inoculata* inasmuch as it differs markedly from the pneumonic form.

3. *For those infections in which the virus enters by way of the mucous membrane and gives rise to metastatic lesions in other tissues of the body, the injection of the virus into the body tissues usually produces an infection; sometimes the essential clinical characteristics of the disease are duplicated, but in other instances a modified infection results quite unlike the spontaneous disease.*

The first and third groups must be looked upon merely as extremes between which there can be no sharp dividing line; for instance, typhoid fever constitutes a somewhat intermediate example. Although *B. typhosus* can infect in moderately small numbers by way of the mucous membrane, nevertheless, living cultures can be injected subcutaneously with the production of nothing more than a local reaction.

The meningococcus, *M. melitensis*, *Treponema pallidum* and the causative organism of poliomyelitis may conveniently be considered together. Injection of monkeys with the virus of poliomyelitis and the accidental injection of man with *T. pallidum* have produced typical infections; similar results could probably be obtained with the meningococcus and with *M. melitensis*, two organisms which produce little or no local lesion on their passage through the mucous membrane.

Small-pox and chicken-pox present important conditions for consideration. When the virus of small-pox is inoculated

§ Personal communication.

on the skin instead of on the mucous membranes, *small-pox inoculata* develops and the disease, as it occurs spontaneously, cannot be reproduced in this manner. According to Hess and Unger⁸ the virus of chicken-pox, when injected intravenously, gives rise to no symptoms but apparently reproduces some immunity.

Exceptional conditions occur in two of the diseases of lower animals. In cattle plague extensive primary lesions occur on the mucous membrane of the intestinal tract and eventually a septicæmia develops. Experimentally the virus behaves in an almost unique manner in that small doses of blood injected subcutaneously set up a fatal infection. Besson¹⁹ states that the influence of the site of injection of the bacillus of symptomatic anthrax is very marked. A dose of the virus which will kill an ox on injection into the cellular tissues of the body will produce merely a benign infection when injected into the connective tissues of the neck, tail or ear and is followed by permanent immunity.

In the preceding discussion the objection may at once be raised that the normal healthy adult can readily withstand the inoculation of a few living and fully virulent pathogenic organisms. A distinct step would be gained if it can be shown that those organisms which normally enter the body through the skin can, as far as injections into the tissues are concerned, set up an infection from the introduction of much smaller numbers than in the case of those micro-organisms which first infect the mucous membranes. In attempting prophylactic immunization against a given disease it is fundamentally necessary to consider the natural portal of entry of the virus in question.

RESUME

An effort has been made to determine whether the virus of measles exists in the circulating blood of a patient, permitting the transfer of the disease from man to man by the inoculation of blood. The prominent data bearing directly on this subject are:

- (1) The successful transmission in two cases previously reported by Hektoen,
- (2) The failure in eight instances recorded in this paper to transmit measles by the injection of blood,
- (3) The clinical phenomenon of the origin of the rash on the face or upper part of the body with its gradual progress downward requiring from one to three days to complete this march.

The symptoms of the two experimental cases that have been reported were not entirely characteristic of the classical type of measles. Although the disease varies extremely little in its clinical manifestations, distinct modifications might readily occur under experimental conditions.

As regards the negative results obtained in these eight individuals, the principle difficulty arises in establishing, by the clinical history, the susceptibility of an adult to a disease so generally prevalent as measles. In some of the men who were inoculated the circumstantial evidence of susceptibility was unusually strong.

Failure to transmit the disease by the injection of blood does not preclude the existence of the virus in the blood stream even in moderate amount. There is some evidence that these men not only failed to become infected but that they were actively immunized by the injection of blood; such an assumption would, of course, presuppose the existence of the virus in the blood stream. Indeed the agent which excites the rash might readily gain access at least temporarily to the blood-stream regardless of whether its distribution takes place by the lymphatics or by the circulating blood.

The constant origin of the eruption on the upper part of the body and its gradual and orderly extension downward is quite unlike the development of eruptions in which the virus is known to be distributed by the circulating blood.

Measles originates as an infection of the respiratory and conjunctival mucous membranes and the virus does not set up metastatic infections in the viscera of the body in the spontaneous disease. Failure to reproduce the disease by subcutaneous injection of the virus is in keeping with the behavior of several other pathogenic micro-organisms of the respiratory and gastro-intestinal tract.

The virus of measles *per se* does not produce serious effects, but one attack of the disease gives rise to a well-marked immunity. With appropriate isolation of the virus it would seem that a substantial active immunity should be obtainable with a minimum of inconvenience to the individual.

CONCLUSIONS

1. The question of the transfer of measles from man to man by the injection of a patient's blood is entirely reopened by the eight successive negative inoculations recorded in this paper.

2. The failure to transmit the disease in this manner does not necessarily exclude the possibility of the occurrence of the virus of the disease in the circulating blood; some evidence was obtained indicating the possibility of producing active immunity by the injection of patient's blood.

This experimental study of measles by the inoculation of volunteers was authorized by General Gorgas and General Ireland at the request of Colonel Frederick F. Russell. The officers and men volunteering for this work signed the following statement:

"I hereby volunteer as a subject for inoculation with measles in order to promote the work undertaken in the United States Army for securing a protective inoculation against this disease."

Having seen the serious consequences of measles in camp life, these men, for no reward to themselves, gladly accepted the risk inherent in these inoculations simply from a desire to be of service. Throughout this work they co-operated cheerfully and conscientiously in carrying out the long isolation essential during these investigations.

The Surgeon General's recognition of their services was made by Colonel Russell in the following letter:

"The Surgeon General has been informed of the fact that you volunteered for the measles investigation. He desires me to express to you his appreciation of the patriotism and devotion to duty that you have shown and to assure you that your contribution to the cause is appreciated by him just as much as was the bravery of the men who went into the fight in France."

It is a pleasure to acknowledge the constant co-operation of Colonel Frederick F. Russell throughout these investigations. I

am especially indebted to Lieutenant-Colonel Channing Frothingham for his assistance at Camp Devens and to Lieutenant-Colonel Henry J. Nichols for his kind co-operation at Camp Meade and at Washington, D. C.

BIBLIOGRAPHY

1. Noguchi, H.: Etiology of Yellow Fever. *Jour. Exper. Med.*, 1919, XXIX; 547.
2. Mayr, F.: Beobachtungen über Masern. *Ztschr. d. k. k. Gesellsch. zu Wien*, 1852, I, 6.
3. Herrman, C.: Immunization against Measles. *Arch. Pediat.*, 1915, XXXII, 503.
4. Hektoen, L.: Experimental Measles. *Jour. Infect. Dis.*, 1905, II, 238.
5. Tunncliffe, R.: Observations on the Bacteriology and Immune Reactions of Rubella and Rubella. *Jour. Infect. Dis.*, 1918, XXII, 462.
6. Anderson, J. F. and Goldberger, J.: Experimental Measles in the Monkey. *Public Health Reports*, 1911, XXVI, 847 and 887.
- Goldberger, J. and Anderson, J. F.: The Nature of the Virus of Measles. *Jour. Am. Med. Assn.*, 1911, LVII, 971.
7. Levy, R. L. and Alexander, H. L.: The Predisposition of Streptococcus Carriers to the Complications of Measles. *Jour. Am. Med. Assn.*, 1918, LXX, 1827.

8. Hess, A. F. and Unger, L. J.: A Protective Therapy for Variella. *Am. Jour. Dis. Children*, 1918, XVI, 34.
9. Richardson, D. L. and Connor, H.: *Jour. Am. Med. Assn.*, 1919, LXXII, 1046.
10. v. Pirquet, C.: Das Bild der Masern auf der Aeusseren Haut. *Ztschr. f. Kinderh., Orig.*, 1913, VI, 1
11. Nicolle, M. and Adil-Bey: Etudes sur la peste bovine. *Ann. de l'Inst. Pasteur*, 1901, XV, 715.
12. Marchoux, Salimbeni and Simond: La fièvre jaune. *Ann. de l'Inst. Pasteur*, 1903, XVII, 665.
13. Ustvedt, Y.: *Norsk Magazin f. Laegevidensk.*, 1906, LXVII, 128.
14. Di Mattei, E.: Beitrag zum Studium der experimentellen malarischen Infection am Menschen und an Thieren. *Arch. f. Hyg.*, 1895, XXII, 191.
15. McNee, J. W., Renshaw, A. and Brunt, E. H.: Trench Fever. *Brit. Med. Jour.*, 1916, I, 225.
- Strong, R. P., et al.: Trench Fever. Oxford University Press, 1918.
16. Besson, A.: Practical Bacteriology. Trans. by Hutchens, H. J., Fifth Ed., 1913, 553.

THE RÔLE OF THE X-RAY IN THE DIAGNOSIS OF LONG-STANDING RENAL TUBERCULOSIS

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The progress which has been made in the last decade in the investigation of diseases of the urinary tract, thanks to the use of the cystoscope and ureteral catheter, has made possible a differentiation of lesions which before that time had been unrecognizable.

There is no disease of the kidney which can be more certainly diagnosed by the use of these modern methods than renal tuberculosis. The demonstration of diminution in the renal function, together with the presence of pus cells and of tubercle bacilli in the catheterized specimen of urine collected from one side, leaves no possibility of doubt as to the condition with which one has to deal.

In the majority of cases a diagnosis is possible by the use of these methods. But in many cases of renal tuberculosis, especially those of long duration, cystoscopy and ureteral catheterization are impossible on account of the changes which have taken place in the bladder mucosa. It may be impossible to recognize the ureteral orifices or they may not admit the ureteral catheter; and there are also some cases in which extensive ulcerative processes have led to such contracture of the bladder as to make the introduction of the cystoscope impossible or too painful for the patient to bear. In many of these cases, although tubercle bacilli may be demonstrable in the bladder urine, owing to the fact that the ureters cannot be catheterized, it is impossible to determine in which kidney the lesion is located, because it must be remembered that in most cases of renal tuberculosis there are a few definite symptoms referred to the kidney itself.

When it is possible to introduce the ureteral catheter, the diagnosis is usually easy, but there are types of long-standing chronic tuberculous processes with sluggish ulceration in which only a few pus cells can be demonstrated and tubercle bacilli may not be found even in repeated catheterized specimens.

In some cases in which the disease has progressed to complete destruction of the kidney terminating in caseation and deposition of calcium salts—the so-called auto-nephrectomy—the deposition of calcium salts will cast a shadow on the x-ray negative varying in density in proportion to the extent of the process. It is in just these cases where for any of the above reasons a definite diagnosis cannot be made that the x-ray will often be the determining factor in the recognition of the lesion.

When the normal kidney substance has been largely replaced by calcified caseation, a complete outline of the kidney and even the ureter may be seen on the x-ray plate and in such cases a definite diagnosis can be made immediately without the demonstration of tubercle bacilli and without recourse to ureteral catheterization except to determine the integrity of the opposite kidney.

It should, therefore, be a routine procedure to precede cystoscopy and ureteral catheterization by plain x-ray examination of the urinary system in all suspected cases of renal tuberculosis.

When the calcification is limited to a single area in the kidney there may be some difficulty in differentiating this process from calculus, but a critical observation of the

density, shape and position of the shadow, will leave little room for doubt. Where the kidney has been completely destroyed, the characteristic lobular appearance of the shadows due to the calcified caseous cavities is very definite and is never seen in any other type of kidney lesion.

By means of stereoscopic plates the individual abscess cavities can be clearly distinguished from each other, provided, of course, that the process has been of a duration long enough to produce deposition of calcium salts in the areas of caseation. Calcification of the ureter is rare, but when it does appear it is perfectly characteristic, the ureter showing on the negative as a dense shadow, the calcification involving the upper portion, the lower portion or indeed its entire course.

In addition to what is shown by the sclerosis of the ureter itself, a shadow may be cast by the caseous material which is sometimes seen filling the lumen of the ureter and which represents the contents of the cavities in the kidneys.

The fact that calcification occurs as a late process in renal tuberculosis and that this calcification will show an opacity on the x-ray plate has long been known, but the practical value of this simple method has been too little emphasized.

During the past few years several cases of renal tuberculosis have been recognized at the Brady Urological Institute from the x-ray plate alone, and a summary of some of the more interesting of these cases will be given in order to emphasize the value of the routine x-ray examination.

CASE 1.—A physician, aged 39, was seen in 1907. The family and past histories were unimportant. The patient had had attacks of dull pain in the back and left flank at the age of fourteen which were diagnosed at that time as indigestion. He first noticed frequency and burning on urination at the age of twenty associated with hematuria. He lost some weight, had chills and fever and was incapacitated for about one year. A careful urinary examination was apparently not done at this time. The blood, however, soon disappeared and the frequency was greatly improved by instillations of silver nitrate. The dull pain in the back and left side, however, persisted, varying in intensity from time to time, and this was the patient's only complaint when he came for consultation.

The physical examination was negative and there was no tenderness in the region of the kidney nor could either kidney be felt. The urine was clear and contained no shreds or pus cells and on this account no examination for tubercle bacilli was made. There was evidence of a chronic prostatitis on rectal examination and the prostatic secretion contained an excess of pus cells.

The patient improved under prostatic massage, irrigation, instillation and dilatations of the prostatic urethra, until the pain completely disappeared. He was then referred to a gastro-intestinal consultant and in the course of an x-ray examination of the gastro-intestinal tract following the ingestion of bismuth a remarkable shadow was seen in the region of the left kidney. This shadow occupied the position of the kidney and showed a definitely lobulated appearance. Nothing similar had been seen at the Johns Hopkins Hospital at this time and a positive diagnosis was not made. Cystoscopic examination showed a normal bladder with the exception that the left ureter could not be seen. The right ureter was easily catheterized and the specimen obtained was normal. A diagnosis of ureteral stricture with destruction of the left kidney was made, but the tuberculous nature of the process was not recognized.

The patient went to a western clinic where a nephrectomy was done and the kidney substance was found to have been entirely replaced by caseation and masses of calcification.

A letter dated April, 1919, states that the patient has been "free from pain and a great deal better since the operation."

The correct diagnosis of this case should have been made from the x-ray alone, but at this time no similar shadow had been seen in the x-ray department. The entirely negative urinary examinations and the fact that the patient responded so well to local treatment were also confusing factors which contributed to the failure to recognize the true nature of the process. (Fig. 1, Case 1.)

CASE 2.—A male, aged 24, consulted Dr. Geraghty in June, 1914, complaining of frequent urination. His father and two uncles had died of pulmonary tuberculosis. The past history was unimportant.

Frequency with burning had existed for the past two years with little or no improvement, at times associated with terminal hematuria. There was also at times a dull aching pain in the back mostly on the left side. A left epididymitis had appeared two years before, followed ten months later by a right epididymitis.

On examination there were no evidences of pulmonary tuberculosis. Neither kidney could be felt. The left testicle was normal; the epididymis was thickened at the globus minor where it was adherent to a scar in the scrotum. The right testicle and epididymis were much obscured and the globus minor was firmly adherent to a scar in the lower portion of the scrotum. The vasa deferentia were normal. The urine contained some pus cells but no tubercle bacilli.

Cystoscopic examination showed a contracted bladder. The mucosa showed some areas of reddening especially in the trigone, but there was no active tuberculosis. The right ureter was seen but it was impossible to catheterize because the cystoscope could not be introduced far enough to permit a ureteral catheter to enter it. The left ureteral orifice could not be seen.

Plain x-ray examination showed a definite dense shadow occupying the region of the left kidney. This shadow suggested a lobular form, but it also presented a somewhat granular appearance. The ureter, which was not enlarged, could also be plainly seen in its entire course from the kidney over the pelvic brim to the bladder.

A diagnosis of left renal tuberculosis was made and nephrectomy was done by Dr. Geraghty. Convalescence was uneventful. The kidney was lobular, twice the normal size and had been entirely converted into a cheesy mass. The ureter was very thick and fibrous, its lumen entirely filled with caseous material and practically obliterated. (Fig. 2, Case 2.)

CASE 3.—A man, aged 24, came for a consultation in June, 1914, complaining of frequent urination. The patient's father and two uncles had died of pulmonary tuberculosis. The past history was unimportant. The patient had first had frequency, strangury and hematuria two years before and shortly after the onset a left epididymectomy was done for epididymitis. A year and a half later the left testicle was removed on account of a persistent sinus.

Since this date the frequency had persisted and there had been pains in the region of the bladder but none in either kidney region.

Physical examination revealed no signs of pulmonary tuberculosis, the left kidney was palpable but not tender. Rectal examination revealed irregular induration of the left lobe of the prostate and seminal vesicle.

Plain x-ray examination showed both kidneys definitely outlined and larger than normal. A definite, rounded mass was seen in the region of the left kidney which closely resembled

the shadow of a stone. On the right side there was a definite, lobulated irregular shadow not so dense as that on the left side but much larger, the process evidently involving the left kidney more than the right.

Cystoscopy showed a reddened trigone and some areas of cystitis but no active ulceration. The ureters were easily catheterized and the specimens from each side contained a few pus cells and a few large colon-like bacilli. The 'phtalein excretion from each side was 18 per cent. No tubercle bacilli could be found in these specimens, nor had any been demonstrated in the bladder urine after repeated examination. A guinea-pig inoculation was also negative.

A *pyelogram* showed a normal right pelvis, the calyces being somewhat elongated, the superior calyx extending as far as the shadow seen on this side. The ureter was not dilated. The left pelvis was normal but the calyces were greatly elongated and extended out so that they more or less surrounded the oval shadow previously seen on this side. The results of this examination tended to support the tentative diagnosis of calcified tuberculous areas in each kidney.

It was decided to explore the left kidney to determine definitely the nature of the shadow. At operation, Dr. Geraghty immediately confirmed the tentative diagnosis from the appearance of the kidney delivered in the wound. On account of the involvement of the right side the kidney was replaced and the wound closed. Convalescence was uneventful. (Fig. 3, Case 3.)

CASE 4.—Physician, aged 41. This patient was seen by us in a base hospital in France having been referred on account of hematuria. His mother had died of pulmonary tuberculosis. His past history was negative except for a left empyema in 1903.

He had noticed blood in his urine first in 1898 and this had continued for about two years with few or no bladder symptoms. The diagnosis of prostatitis had been made and local treatment given. In 1902, blood had reappeared in his urine and continued for a short time. In 1906 for the same symptom the patient had gone to a western clinic where cystoscopy was performed but it was found impossible to catheterize the right ureter. From this time on the same slight frequency of urination had persisted. Following the exposure incident to foreign service the hematuria had reappeared in October, 1918. Physical examination was negative except for the scar of the empyema operation. Examination of the urine showed numerous pus cells and red blood cells but no tubercle bacilli.

Cystoscopic examination showed a small ulcerated area on the anterior bladder wall and rather marked injection of the trigone. The left ureter was readily catheterized but no definite right ureteral orifice could be made out in spite of repeated attempts. The urine from the left kidney was normal.

A definite diagnosis could not be made but tuberculosis of the right kidney was suspected and the patient invalided home to the States for further study.

On entrance to the Brady Urological Clinic after repeated examination of the urine a few tubercle bacilli were found, the cystoscopic findings were corroborated and the plain x-ray examination showed a clear outline of both kidneys, the right kidney being smaller and the shadow remarkably opaque. On careful observation a definite dense lobulated appearance was seen and the ureter which was distinctly opaque could be easily made out in its course to the bladder.

In the plain x-ray of the pelvis the lower end of the right ureter showed the same distinct opacity and its shadow could be seen coursing over the brim of the pelvis. The outline of the left kidney showed no opacities and the organ could be definitely seen to have undergone compensatory hypertrophy.

From the characteristic dense lobular shadows seen in the plain x-rays and the demonstration of tubercle bacilli in the

urine a diagnosis of right renal tuberculosis was made and a nephrectomy was performed by Dr. Geraghty, December 13, 1919. Convalescence was uneventful.

The kidney was found to be entirely destroyed, all kidney substance having been replaced by caseated masses separated from one another by thin layers of fibrous tissue. The ureter was entirely obliterated.

This case was evidently one of very long standing, slowly progressing, the initial symptoms dating back twenty years. In spite of this long duration the bladder had become only very slightly involved and tubercle bacilli were found only on one occasion among many examinations.

It is this type of slowly progressing lesion which results most commonly in the so-called auto-nephrectomy and it is in just this class of lesions that calcium salts are deposited in amounts large enough to permit a diagnosis to be made from the plain x-ray plate positive. (Fig. 4, Case 4; Fig. 5, Case 4.)

CASE 5.—A man, aged 46, entered the Brady Urological Institute in May, 1919, having been referred with a diagnosis of left renal tuberculosis. His family history was negative. At the age of nineteen an abscess of the left testicle had been opened and eighteen months later two abscesses had been opened in the right lumbar region. Six years before he came to us a severe attack of renal colic on the right side had been followed by the passage of a small calculus and four years later a similar attack occurred on the same side. There had been no frequency, hematuria or pain on urination, but the patient had had a dull aching pain in the region of the left kidney and soreness in the left hip for the past few years. The patient was seen about one year before but the left ureter could not be catheterized.

Physical examination was negative except for slight tenderness elicited on deep pressure over the left kidney. Neither kidney could be felt on account of the thick abdominal wall. The scars of the old abscesses in the right lumbar region were well healed. The urine was clear, contained no pus cells and no tubercle bacilli.

Stereoscopic x-ray plates were taken of the left kidney and the whole organ was represented by a series of lobulated shadows which without doubt represented the calcification of the individual areas of caseation. Nine such lobules could be easily counted on the stereoscopic plates. The shadow of the right kidney showed that it had undergone compensatory hypertrophy. There were also evidences of an old healed tuberculous process involving the first, second and third lumbar vertebrae. The total function as measured by an intramuscular injection of 'phtalein was normal. The patient was advised to return later for nephrectomy.

Although operation has not as yet been carried out on this patient there can be no doubt as to the diagnosis or as to the integrity of the right kidney. One may also assume that the left ureter has been occluded and that the process commonly called auto-nephrectomy has also occurred in this case. (Fig. 6, Case 5.)

A dogmatic classification of the shadows cast by various types of tuberculous kidneys cannot be made and all gradations may occur, from the small indefinite shadow cast by a calcified, tuberculous area about a calyx, to the beautiful lobulated shadow which results from a completely destroyed kidney, consisting entirely of calcified abscess cavities. The x-ray of such a kidney is quite unmistakable, but the smaller, indefinite shadows which may be seen are occasionally difficult to differentiate from renal calculi and also from various extrarenal shadows such, for example, as the contents of the intes-



FIG. 1 (Case I).—Characteristic lobulated appearance of a kidney completely destroyed.



FIG. 3 (Case III).—Complete destruction of the upper pole with beginning deposition of calcium salts in lower pole of a kidney not yet completely destroyed.



FIG. 2 (Case II).—Typical mottled appearance due to irregular deposition of calcium salts in a kidney completely destroyed. The outline of the ureter is plainly seen.



FIG. 4 (Case IV).—Completely occluded kidney with deposition of calcium salts throughout its entire extent.

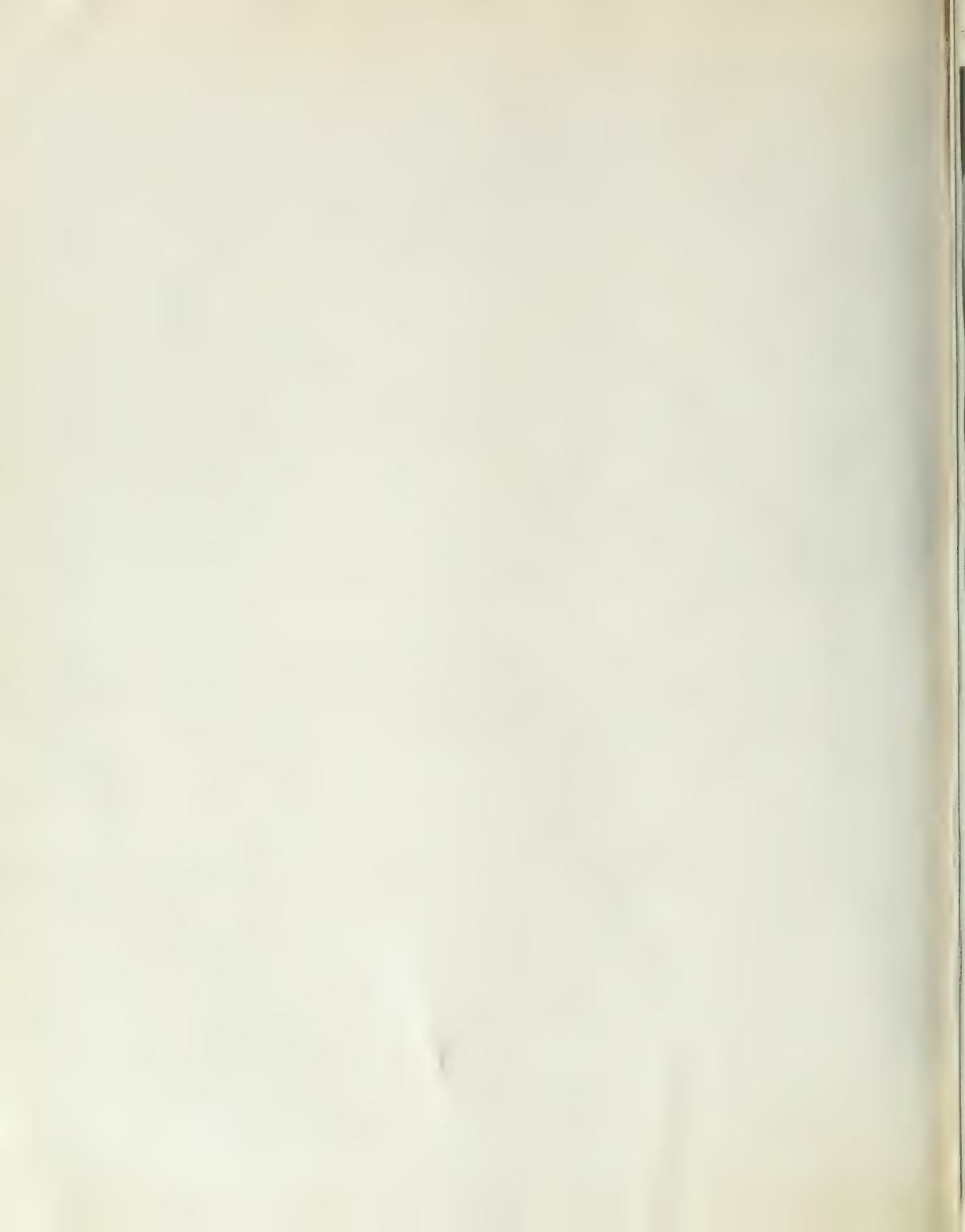




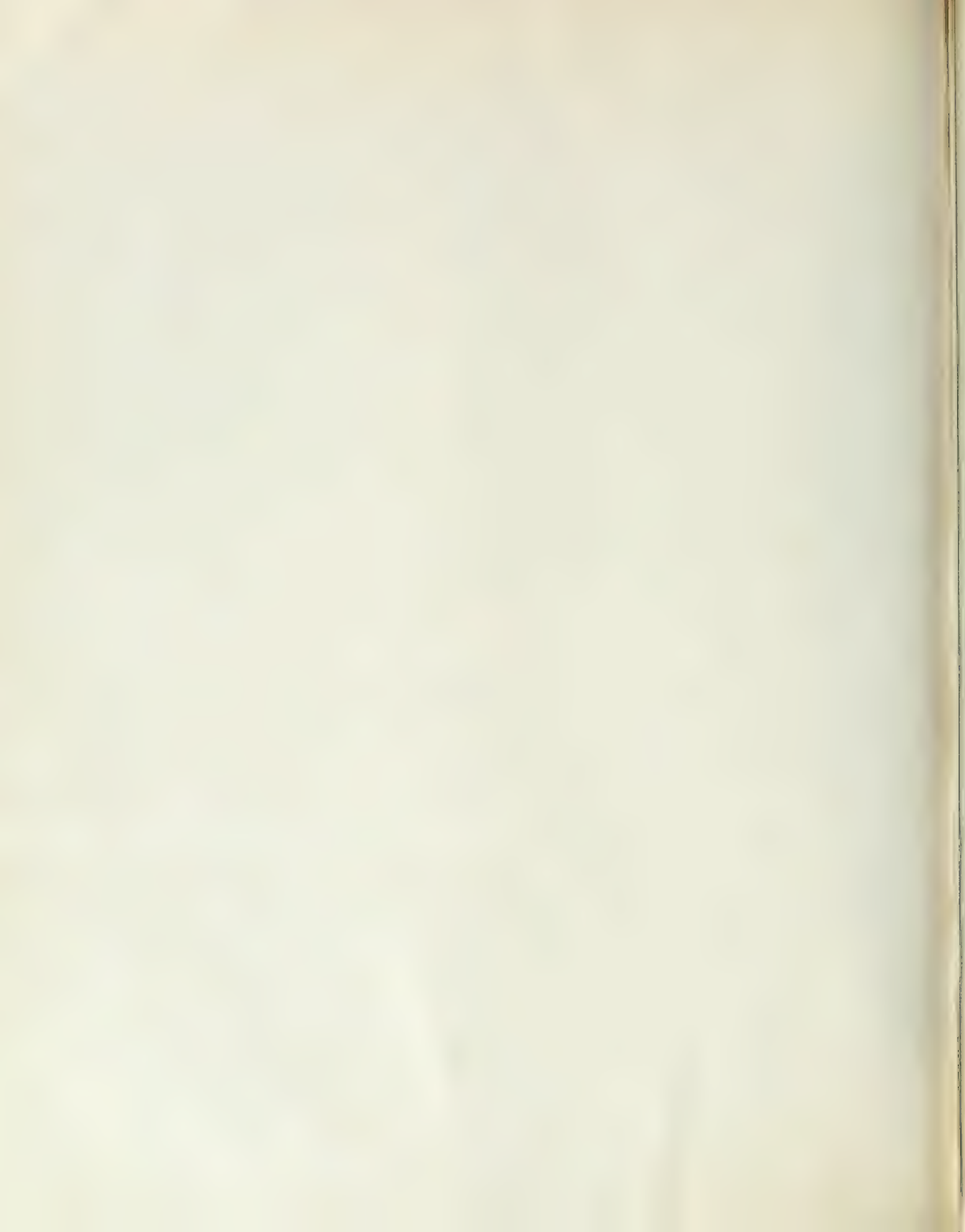
FIG. 5 (Case IV).—Calcification of the lower end of the ureter in Case IV. Same side.



FIG. 7.—Drawing of the stereoscopic plates of Case V, showing the clear differentiation of the individual calcified lobules.



FIG. 6 (Case V).—Kidney completely destroyed, showing typical lobulated form with deposition of calcium salts in the caseated areas. Old healed tuberculous process of the twelfth thoracic and first and second lumbar vertebræ.



tine, calcified glands, gallstones, etc. It must also be remembered that the extent of the shadow on the x-ray plate does not represent the extent of involvement of the kidney and many kidneys have been seen, on removal, totally destroyed, which, on x-ray examination, showed only small indefinite shadows, or none at all.

The presence of a true renal calculus, in association with renal tuberculosis is rare, but several such cases have been seen in which a calcium oxalate stone occupied the pelvis of a tuberculous kidney. In all probability such a stone arises from the deposition of calcium salts in a tuberculous ulceration of a calyx. We have seen several cases of early tuberculosis in which the only focus found in the kidney after the operation was an ulceration of a single calyx. In a few of these cases there was a definite deposition of calcium salts and it is easily conceivable that a small portion of such a calcified area could break off, fall into the pelvis and form the nucleus of a large stone.

Such a stone gives a picture quite different from that occasionally encountered when a tuberculous area in a kidney, wrongly diagnosed as a stone, is exposed at operation. If an attempt is made to remove the supposed stone it will be found to consist of a grumous, putty-like material which cannot be taken out as a whole. If such a condition is encountered and its true nature recognized at operation, it is far better to do a nephrectomy provided previous studies have demonstrated that the remaining kidney is normal. However, if the x-ray shows the presence of similar areas in the remaining kidney or if the evidence of its involvement has been demonstrated, no operative procedure should be attempted, as the trauma incident to operation may very readily convert a slowly progressing, partially walled-off process into an acute exacerbation or may even lead to a general miliary tuberculosis.

It is not the purpose of this paper to discuss the very great assistance of the data which may be obtained from the pyelogram and cystogram. In an occasional case when sufficient information cannot be obtained by other means, a diagnosis can be made by these studies. It has been the practice at the Brady Clinic, however, to refrain from a pyelographic study if a definite diagnosis of renal tuberculosis can be made by the usual methods. There have been no bad results following this method but we have not felt that in cases where the diagnosis was already certain the additional instrumentation was justified.

CONCLUSION

(1) X-ray studies of the entire urinary tract should be carried out in all cases of suspected renal tuberculosis.

(2) In some cases, when other methods of examination have failed, a definite diagnosis of renal tuberculosis can be made from the plain x-ray alone but, whenever possible, catheterization of the other ureter should be done to establish the integrity of the opposite kidney.

(3) The shadows depend entirely upon the amount of calcification which has taken place in the diseased kidney.

(4) Various types of shadows may be seen in the plain x-ray of a tuberculous kidney varying from the indefinite shadows cast by small areas of calcification to the characteristic lobulated shadow which is typical of a completely destroyed kidney.

(5) Pyelography and cystography may clear up the situation in some cases but these procedures should not be carried out if a diagnosis can be made by other and simpler methods.

NOTE.—Since this article was written a paper by Braasch and Olson (Roentgenographic Diagnosis in Renal Tuberculosis, Surgery, Gynecology and Obstetrics, XXVIII, 6, p. 5551) has appeared in which virtually the same conclusion has been reached.

BIBLIOGRAPHY

1. Sträter: *Zeitschr. f. Röntgenk.*, 1908, p. 41.
2. Mankiewicz: *Deutsche Med. Woch.*, 1908, p. 1290.
3. Grässner-Hürter: *Zeitschr. f. Röntgenk.*, 1910, p. 376.
4. Fenwick: The value of expert radiography and cystoscopy in the detection of obsolesced tubercle kidney. *Brit. Med. Jour.*, July 3, 1919, Vol. 2, p. 16.
5. Dietlen: *Zeitschr. f. Röntgenk.*, 1911, p. 85.
6. Casper: *Zeitschr. f. Urol.*, 1913, VII, p. 532.
7. Marion: Une nouvelle cause d'erreur dans la radiographie des calculs du rein. *Jour. d'Urol.*, 1912, 1, p. 655.
8. Papin: Localisation de la tuberculose rénale par la radiographie. *Archives urologiques de la clinique de Nechar*, fasc. 2, juin, 1913, p. 177.
9. Heitz-Boyer: Exclusion partielle dans un rein tuberculeux avec urines claires. *Jour. d'Urol.*, 1914, V, p. 297.
10. Pilliet: Tuberculose rénale à forme anormale. *Jour. d'Urol.*, 1914, V, p. 595.
11. Legueu, Papin and Malngot: Exploration radiographique de l'appareil urinaire. Paris, 1913.
12. O'Neill: Renal tuberculosis. Cabot's *Modern Urology*, Vol. II.
13. Raffine: Tuberculose rénale. *Encyclopédie Française d'urologie*, Paris, 1914, t. 2.

REPRINT OF THE OSLER NUMBER OF THE BULLETIN

The demand for copies of the Osler number of the Bulletin has exceeded the number of copies printed. Should a sufficient number of requests for additional copies of this number be received by October 1st to justify another issue, it will be reprinted and sold for \$1.00 per copy. All those interested in securing copies should send in their orders promptly to

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IN MEMORIAM

ADMONT HALSEY CLARK

By WILLIAM G. MACCALLUM

A memorial meeting was held on June 9, 1919, in the lecture room of the Pathological Laboratory of The Johns Hopkins University to uncover a tablet placed there by colleagues and friends to the memory of Dr. Admont H. Clark, associate professor of pathology, who died on October 13, 1918. The admiration and affection of all who had known him were expressed in brief addresses by Dr. Welch, Dr. Howell, Dr. Sabin and Dr. MacCallum. The following short biographical sketch was read:

Admont Halsey Clark, the eldest child of Cyrus Alonzo and Harriet Gulick Clark, was born near Kyoto, Japan, on August 25, 1888. His father, who came from Genesee County, New York, had graduated as a minister at Oberlin College. His mother, whose family, the Gulicks, had for generations been missionaries, was born in the Caroline Islands.

Their married life has been almost entirely spent in missionary work in Japan and there Admont lived and went to school until he was 12 years old. After that he was sent to America to be educated and came to live with his mother's sister and her husband, who is Professor Jewett, of Oberlin College. With them he remained through his school and college life, becoming deeply attached to this aunt and uncle who in some degree took the place of his distant parents.

All through his student career, both at Oberlin and later in the medical school, he earned money by every kind of outside work to support himself. Nevertheless, he found time enough for his studies to stand well in his classes, and playtime enough to excel at athletic sports. He was a particularly good player at football and was on the University and the Maryland State teams. Music, too, he loved and during this whole time he studied the violin and learned to play it very well, so that later he derived great pleasure from taking part in trios and quartets.

After his graduation at Oberlin College in 1910 he formed one of a party of biologists on an expedition to Point Pelee on Lake Erie to observe the migratory flight of birds and to learn whether they flew boldly across great bodies of water or tried to take advantage of the islands scattered across the lake. Here he contracted typhoid fever which was so severe that he lost a whole year before entering The Johns Hopkins Medical School in 1911. During part of this time, however, he acted as assistant in chemistry at Oberlin College.

When fully recovered, he began work with a new zest. At college he had taken up scientific subjects, showing especial interest in chemistry toward which he had probably been led by Professor Jewett. Again he stood high in his class and, in addition, he proved to be one of the men who can and must work on special problems which carry them beyond the routine work of the class.

Each year he seems to have been hard at work on one or more problems, as his published papers show. In the first year he worked under Dr. Sabin's direction on the development of the lymphatics, in the second under Dr. Whipple on the chemical tests of the function of the liver. In his fourth year he substituted as interne in the hospital for two months and there devised and worked out a method for studying venous pressure in disease. He graduated with the degree of Doctor of Medicine in 1915 and entered immediately the department of pathology where each year he advanced, beginning as an assistant and becoming successively instructor, associate and associate professor of pathology.

In these positions he showed his ability to carry out serious investigations independently and proceeded to a long and most laborious study of the internal secretion of the pancreas in its relation to sugar metabolism. This was brilliantly successful in demonstrating the presence of a secretion essential to the consumption of sugar by the beating heart.

Next he turned to the study of the filtrable toxin which he and Felton had produced by growing the hemolytic streptococcus in blood. They completed and published a short paper on this subject, but much more work was planned to control and confirm their results. At the same time and before this he was working in a more leisurely way on the effect of diet upon the healing of wounds and had obtained some interesting results which were left in the form of notes from which Mrs. Clark has written and published his paper.

He was married at Portland, Maine, on July 9, 1917, to Miss Janet Howell, and his daughter, Anne Janet, was born on May 15, 1918. This was a year of extraordinary happiness for him. Since December, 1917, he had held a commission as first lieutenant in the medical reserve corps of the army and was very anxious to be assigned to active service, but the surgeon-general's office, recognizing the importance of his work on the streptococcus, supported it generously and kept him in Baltimore. In the autumn there came the epidemic of influenza and he was one of the many stricken. He appeared to recover from its first effects and returned to the laboratory for a day or two, but then developed a streptococcal pneumonia from which he died on October 13, 1918. His loss was among the greatest caused by that terrific epidemic.

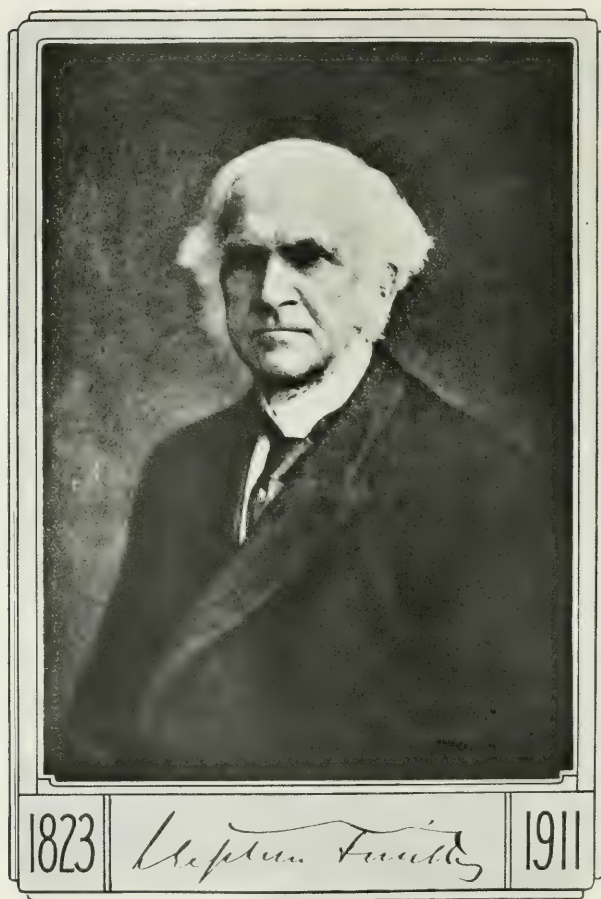
Clark was a young man, prematurely slightly gray with an honest face and bearing which captivated everyone at once. He was so intelligent, so completely trustworthy and so efficient that there was never any hesitation in entrusting to him, when occasion demanded, the whole charge of the department, nor was there the slightest doubt of the propriety of his extraordinarily rapid advancement to the place of associate professor only three years after his graduation from the medical school.



ADMONT HALSEY CLARK.







Aside from his undoubted ability in the routine work of such a department and his deserved popularity among the students and assistants who recognized at once his value as a teacher, he had a great talent for the investigation of the problems which interested him. Genius is a much misused word and can hardly be applied to Clark, because he was essentially well balanced and sane and went about his work upon a carefully devised plan which partook of genius only in that he had great enthusiasm, an almost unlimited capacity for concentrated work and a remarkable quality of efficiency. He worked early and late, even moving a bed into one of the rooms of the laboratory in the summer, when his wife and child were away, so that he could stay there continually and watch his experiments at night. When he constructed apparatus with much difficult glass-blowing and grinding of stopcocks, it worked. When he carried out a series of experiments to prove a point, they worked and there were few if any false steps. Foresight and rational judgment as to the relative importance of necessary evidence helped him greatly to advance. His problems were large and complicated and their solution involved long and difficult experiments—especially in the case of the pancreatic secretion, where he had to perfuse a surviving pancreas and a surviving and beating heart, analyzing the fluid from time to time as it passed; and it was only with very perfect apparatus, all of which he constructed himself, that it could be done. It was thoroughly good work and full of the most brilliant promise. He was only 30 when he died.

His interests were by no means limited to the laboratory. He loved the outdoor life, and all games and sports, but more

especially, perhaps, the life of the woods with shooting and fishing. His vacations during his course at the medical school were spent working at summer camps for his uncle, Dr. Luther Gulick, and his honeymoon was a camping and fishing trip on Lake Temagami. He seems to have had the same skill in everything he did in the woods that he showed in the laboratory.

His loss is a very great one not only to us who knew and admired him, but also to science. He seemed destined to do great things.

His published papers were as follows:

On the Fate of the Jugular Lymph Sacs and the Development of the Lymph Channels in the Neck of the Pig. *Amer. Jour. of Anatomy*, 1912, XIV, 11.

Tests for Hepatic Function and Disease Under Experimental Conditions. (Whipple, Peigalt & Clark.) *Johns Hopkins Hosp. Bull.*, 1913, XXIV, 243.

A Study of the Diagnostic and Prognostic Significance of Venous Pressure Observations in Cardiac Disease. *Arch. Int. Med.*, 1915, XVI, 587.

The Interrelation of the Surviving Heart and Pancreas of the Dog in Sugar Metabolism. *Jour. Exp. Med.*, 1916, XXIV, 621.

The Same. Second Paper. *Ibid.*, 1917, XXVI, 721.

A Filtrable Toxin Produce of the Hemolytic Streptococcus. (Clark and Felton.) *Jour. Amer. Med. Assoc.*, 1918, LXXI, 1048.

The Effect of Diet on the Healing of Wounds. *Johns Hopkins Hosp. Bull.*, 1919, XXX, 117.

REMINISCENCES OF TWO EPOCHS—ANÆSTHESIA AND ASEPSIS

By STEPHEN SMITH, A. M., M. D., LL. D., New York

The development of an art is characterized by a succession of events each of which signifies progress. These events may, singly, appear unimportant, but, as Sir James Paget truthfully remarks, "Closely studied they are links in an endless chain of events leading to a higher development as we witness in the embryo." In this chain of events there occasionally occurs one which far transcends others in the radical and fundamental changes which it effects in the practice of the art under review. It stands a beacon light which illumines with ever-increasing brilliancy the pathway of the humblest practitioner. Such an event creates an epoch—"A point of time from which succeeding years are numbered" (Cent. Diet.).

Baas, the eminent historian of medicine, regards epochs as the essential features of the development of an art and from an educational viewpoint urges that they be studied by every practitioner. Impressively he remarks:

An acquaintance with the views and knowledge of epochs submerged in the shoreless ocean of time, frees the mind from the fetters and currents of the day with its often oppressive restraints, widens the horizon for a glance into the past, and an insight into the present of human activity, deepens the view for a comprehension of the ideas which guided the earlier and more recent

physicians, and gives on the other hand to our daily professional labor a high consecration.

Though two of the most remarkable epochs in the history of surgery—anaesthesia and asepsis—occurred within my personal experience, it is unfortunately true that with the profession at large the views and knowledge of these great events have long been submerged in the shoreless ocean of time.

This general ignorance of the great events in the recent history of surgery is due to the failure of the schools to include in their courses of instruction a well-devised system of teaching the "views and knowledge of epochs." No department of science has a more interesting and instructive history than medicine, inasmuch as every advance tends to the betterment of the race. My experience as a teacher for many years emphasized the fact that students are not only greatly interested in historical incidents connected with the subject, but that those incidents proved suggestive to the memory when the subject was recalled in actual practice in later life.

Deeply impressed with the truth and moral significance of the historian's sentiments and their quite general application, it has occurred to me that it would be peculiarly appropriate to the present occasion if I recalled some of my experiences

and observations on the introduction of these two greatest epochs in the history of surgery.

ANÆSTHESIA

OCTOBER 16, 1846

When I entered the office of Prof. Frank H. Hamilton, of Buffalo, New York, in May, 1847, as a student of medicine, anæsthesia was on trial. Though it bore the imprimature of the surgeons of the Massachusetts General Hospital, headed by the honored name of Dr. John C. Warren, several deaths had been reported during its use, which served to make conservative surgeons cautious. Prof. Hamilton was of that class and he resorted to anæsthesia only occasionally and in cases believed to be especially adapted to its use. This fact gave me ample opportunity to compare the old-time method with that promised by the new discovery.

The first operation without anæsthesia that I witnessed was so disquieting on account of the sufferings of the patient that I was nearly driven from the profession. Its cruelty was so shocking to my untrained nervous system that I begged to be excused from attending another operation, but the professor made merry of my sensitiveness, assuring me that the most successful surgeons had fainted at the first operation but that in the "long run" extreme sympathy for the patient made a cautious and conservative operator. The case referred to illustrates the ordinary operative proceedings in hospital practice at that time:

The patient was a workman from a shop and was suffering from a strangulated hernia. No other preparation was made than to remove his exterior clothing and sponge the surface over the hernia. The surgeon came in haste, put on a hospital apron and urged haste in bringing the patient to the table. Several strong-armed attendants were selected to hold the patient if he made resistance. With a conspicuous display of the knife the surgeon made his first incision with lightning rapidity which was followed by the violent screams and struggles of the patient and a volley of oaths. It required several minutes to place him again in position and meantime the surgeon, with knife poised in the air, awaited nervously an interval when he could cut twice in the same place. A second incision intensified the shrieks and efforts of the patient to escape from the table. All was now indescribable confusion, but the attendants succeeded in overcoming the patient now exhausted by his struggles and shock and at length the exciting tragedy came to an end, with all parties completely exhausted.

That this is not an overdrawn description of every day operations in the great hospitals of the country I will quote a reliable author's experience, the patient being a woman:

She is cheered by kind words, and the information that it will soon be over. . . . She is enjoined to be calm and to keep quiet and still. . . . But of what avail are all her attempts at fortitude! At the first clear crisp cut of the scalpel, agonizing screams burst from her and with convulsive struggles she endeavors to leap from the table. But the force is nigh. Strong men throw themselves upon her and pinion her limbs. Shrieks upon shrieks make their horrible way into the stillness of the room until the heart of the boldest sinks in his bosom like a lump of lead. At

length it is finished, and prostrated with pain, weak from her exertions and bruised by the violence used, she is borne from the amphitheatre to her bed in the ward to recover from exhaustion.

The screams and struggles of patients submitted to operation, which we then heard and witnessed, were but the echo down the ages of those heard when the primitive surgeon first applied the "chipped-knife" to human flesh to remove the broken fragment of a war missile. There were screams and struggles in the home of Moses when Zipporah, his highbrow Midianite wife "Took a flint and cut off the fore-skin of her son" (Ex. iv. 24). There were abundant screams and struggles in the Jewish families when "Joshua made himself knives of flint and circumcised the children of Israel" (Joshua v. 3).

Pain and suffering was regarded as the chief obstacle to success in operative surgery from the time of that first operation with the knife or flint. Even Hippocrates, in lofty phrase, expressed the prevailing sentiment: *Divinum est opus sedare dolorem*.

Two methods of mitigating suffering seem to have been suggested to primitive surgeons, viz.:

1. Celerity of operation to diminish the time of suffering, and,
2. The discovery of an agent which would safely cause insensibility.

CELERITY OF OPERATION

Of these two methods the first was the most practical, as it involved no danger, and was, therefore, adopted at once. Successful celerity of operation required two conditions: (1) Such a variety of instruments as may be necessary to meet promptly every possible emergency; (2) Dexterity in the use of instruments. Fortunately the early Huns and Egyptians, by nature and training, were especially adapted to devise the instruments and use them dexterously—conditions necessary to success in celerity of operation.

In the field of invention the oriental excelled. Centuries before the Christian Era we have descriptions of instruments in familiar use by Hindus and Egyptians which in perfection of finish and adaptation to special uses are equal to the "kit" of the modern surgeon. For example, the forceps devised to extract the fragments of the rude missiles employed in the tribal wars were thus described by a contemporary writer:

They ought to be about nine inches long; their mouths be respectively like those of a lion, tiger, wolf, hyena, bear, elephant, cat, hare, antelope, crow, heron, dog, jay, vulture, falcon, owl, kite, cock, crouch, the bee, rat, mouse or bullock. Each half must be united to the other by a nail of the form of a lentil seed being bent inwards at the handles like the elephant-driver's hook.

There was also the same great variety of probes and tubular instruments each being designed to meet a special emergency during the operation. The following directions in preparation for an operation illustrate the care exercised by the primitive surgeon to render a rapid operation safe:

A surgeon contemplating to operate . . . should first have ready the following: blunt instruments (forceps, etc.), sharp instruments, potential cauteries, horns, catheters, leeches, a dry

gourd, a cauterizing needle, stuffing materials, fat, milk, oil, string, board, bandage, honey, soothing decoctions, injections, lotions, fan, cold and warm water, a frying pan, able, steady and attached servants. During the operation let the patient be seated, who has taken very little food, offered sacrifices and made ablutions, with his face towards the East. The surgeon should stand with his face toward him and plunge his instrument after the proper incision until matter comes out, and withdraw it, avoiding vital parts, vessels, muscles, articulations, bones and arteries . . . Boldness, rapidity of action, sharp instruments, operation without trembling, fear or doubt, are always praiseworthy of the surgeon.

As a "show-*lad*" dexterity in the use of instruments was at its climax when I entered the profession. At hospital clinics attended by students operators performed fantastic tricks with instruments often brandishing them in the air when about to make an incision. An amputation was a favorite occasion for these displays of dexterity. The Catlin, glittering for a moment above the head of the operator, was plunged through the limb and with one artistic sweep made the flaps or completed a circular operation. After several aerial gyrations the saw severed the bone as if driven by electricity. The fall of the amputated part was greeted with tumultuous applause by the excited students. The operator acknowledged the compliment with a formal bow. The clinics of these operators were as popular as theatrical performances and about as instructive.

Celerity of operation as I witnessed it, while accomplishing little in the mitigation of the sufferings of the victims of operation, often had very serious features. Wounds of blood vessels and nerves, puncture of viscera and similar accidents not unfrequently occurred in the clinics of operators famous for the display of dexterity and celerity. The movement of a struggling patient at the moment the operator plunged his knife resulted in wounding the femoral artery. Puncture of the urinary bladder and intestines, division of important nerves and similar accidents were reported from clinics. These accidents usually were the interesting feature of the operation, as they tested the ability of the operator to meet the emergency. The accident itself did not reflect upon the operator's skill but was attributed to the unfortunate movement of the patient at that critical moment when the surgeon was to exhibit his dexterity. Thus the tragedy that resulted in a coroner's inquest contributed to the reputation of the operator as a most skillful surgeon.

AN ANÆSTHETIC

Allusions to the use of "pain-killing" agents are frequent in medical history from prehistoric periods. In general their discovery has been accidental as in the case of gases from the earth. More frequently the narcotizing agent was found in vegetables, the poppy, the mandragora, belladonna, hyoscyamus, cannabis Indica, etc. Cutting operations without pain under the narcotizing effect of these vegetables are mentioned by many writers at different periods. Homer describes two operations in that picturesque style which suggests that he must have been present and witnessed them. He says:

Machon was summoned to remove an arrow which was driven through the belt of Menelaus, King of Sparta; he extracted the

arrow from the well-fitted belt, but while it was being extracted the sharp barbs were broken; then he loosed the variegated belt and the girdle beneath and the plated belt beneath, which the brass-workers had forged, when he perceived the wound where the bitter shaft had fallen; having sucked out the blood, he skillfully sprinkled on it soothing remedies.

Euryppus wounded with an arrow in the thigh called upon Patroclus to remove it. Patroclus, laying him at length, cut out with a knife the bitter, sharp arrow from the thigh, and washed the black blood from it with warm water. Then he applied a bitter pain-assuaging root, rubbing it between his hands, which checked all his pains; the wound indeed dried up, the bleeding having ceased.

The following prescription for making the famous anæsthetic of Theoderic (1278) illustrates the efforts to discover an anæsthetic:

Take of opium and the juice of unripe mulberry, of hyoscyamus, of the juice of the hemlock, of the juice of the leaves of the mandragora, of the juice of the wood ivy, of the juice of the forest mulberry, of the seeds of lettuce, of the seed of the burdock, which has large and round apples, and of the water-hemlock, each one ounce; mix the whole of these in a brazen vessel, and then in it place a new sponge, and let the whole boil, and as long as the sun on the dog-days, till it [the sponge] consumes it all, and let it be boiled away in it. As often as there is need of it, place this same sponge in warm water for one hour, and let it be applied to the nostrils till he who is to be operated on has fallen asleep and in this state let the operation be performed. When this is finished, in order to rouse him place another dipped in vinegar, frequently to his nose. Or let juice of the roots of fenigreek be squirted into his nostrils. Presently he awakens.

The story of the researches and efforts to discover a reliable and safe anæsthetic does not differ from that attending the introduction of all great epochs. Repeatedly the discovery was announced and the prize seemed won, only to be followed by a disappointment the more depressing because so often repeated. Indeed, these disappointments had so crystallized professional opinion against the possibility of discovering a safe and reliable anæsthetic that on the very eve of its announcement the most eminent surgical authority of the period, Velpeau, thus voiced the prevailing sentiment of the profession (1839):

To escape pain in surgical operations is a chimera which we are not permitted to look for in our day. A cutting instrument and pain in operative medicine are two words which never present themselves, the one without the other, in the mind of patients, and it is necessary for us surgeons to admit their association.

It is creditable to the profession that the chief obstacle to an earlier discovery of a safe and reliable anæsthetic was the fear of fatal results in making the necessary tests on human subjects. Rice, author of the "Trials of a Public Benefactor," remarks:

It is probable the deadly results which must have often ensued from their use, the long-continued depression which they exert upon the nervous system, the confirmed stupor and the congestions and other accidents which are so liable to follow, all conspired to prevent their use, or even examination.

The only interesting feature in the centuries of search for an anæsthetic relates to the incidents by which the inhalation

of nitrous oxide gas (laughing-gas) led to the discovery of scientific anesthesia. In 1799, Sir Humphrey Davy, then an assistant in the "Pneumatic Institution" of Dr. Beddoes, Penzance, England, experimented with nitrous oxide gas and described in a familiar way its exhilarating and intoxicating effects. He even used it for the relief of pain in the head and teeth and finally suggested its possible use in surgical operations:

As nitrous oxide in its extensive operations seems capable of destroying physical pain, it may probably be used with advantage in surgical operations in which no great effusion of blood takes place.

The suggestion of Davy was so natural that it is surprising that nearly half a century elapsed before the subject again attracted attention, though nitrous oxide (laughing-gas) was in popular use for amusement in social circles.

The circumstances attending the actual employment of nitrous oxide to allay the pain of a surgical operation not only fulfilled Davy's prediction, but gave to our country the great honor of discovering a safe and reliable anæsthetic and also of placing anæsthesia on a scientific basis.

Dr. Crawford Williamson Long (1815-1878) of Danielsville, Ga., a graduate of the medical department of the University of Pennsylvania, was impressed, while attending an exhibition of "laughing-gas," with its power of causing a harmless delirium, and ventured to test its effects personally. In his performances under its influence he received a painful injury of his leg of which he was not conscious until he had recovered from the effects of the gas. Like Davy he became imbued with the idea that surgical operations might be performed without pain while a person was in this state of delirium. Long seems to have been a very unpretentious practitioner of his profession in a small rural town quite remote from even the current medical topics. He engaged in general practice and performed all the surgical operations that came under his observation. In 1842 he first operated on a patient under the control of nitrous oxide and removed a tumor from the neck of a lady without pain. Subsequently he used this gas in his operations but did not think the method of sufficient importance to publish an account of it until the question of priority of discovery of an anæsthetic became the subject of Congressional inquiry on the petition of Dr. W. T. G. Morton, of Boston, 1847.

In 1844 nitrous oxide attracted the attention of Horace Wells, a dentist of Hartford, Conn., in the same manner it had Davy and Long, while being used as a "laughing-gas." Wells tested it by having a tooth extracted while under its influence and on returning to consciousness, exclaimed: "A new era in dentistry." He adopted it in practice and related his experience to Dr. W. T. G. Morton, a dentist of Boston and former partner in business. Morton was an enterprising young man who recognized the importance of the new treatment, if it really proved to be capable of accomplishing the objects claimed. He, therefore, thoroughly tested it and became convinced of its value in the practice of dentistry, the logical result of this conclusion being that it would prove

equally valuable in the field of operative surgery. To test this question by high authority Morton applied to Dr. John Collins Warren then at the head of the surgical staff of the Massachusetts General Hospital. The day fixed for a trial operation was October 16, 1846. The operation was advertised widely and a notable gathering of the most distinguished members of the profession in Boston and vicinity was in attendance.

Prior to the date of the operation Morton had been advised by a chemist, Dr. Jackson, that sulphuric ether had the same effect as nitrous oxide and was more manageable. Accordingly Morton prepared to give this gas which occasioned a few minutes delay in his arrival at the hospital. This delay was construed by the skeptics in the audience as a complete failure of Morton to meet the test, and when he appeared a few minutes later he was greeted with derisive laughter. Even Dr. Warren had apologetically informed the audience that he had little faith in the alleged anæsthetic.

The operation, the removal of a vascular tumor of the neck, was a complete success. A profound silence fell upon the witnesses of a great epoch in surgery as Dr. Warren declared in homely phrase, "Gentlemen! This is no humbug." This announcement, heard around the world, ushered into human history the great epoch—ANÆSTHESIA—freedom from pain in the practice of operative medicine.

ASEPSIS

1867

The discovery of a safe and reliable anæsthetic seemed to cut the cords which restrained the progress of operative surgery and this branch of practice went forward in leaps and bounds. Medical periodicals were filled with descriptions of new, unheard of, and even unthinkable operations, and the clinics became interesting for the novelty of the operations and the perfection of details, now so much more carefully completed.

THE ANTISEPTIC PRINCIPLE

1867

But important as was the reform in the manual of the operation, it was painfully apparent that in the final summary of results the mortality of operated wounds had not diminished. The chief element of disaster, suppuration, still remained in full force and determined by its relative intensity the final result. Of this fact I had an opportunity for ample experience. On entering the Bellevue Hospital Resident Staff (1850) my duty as the junior member was to carry the "pus-pail," the receptacle into which the senior surgeons placed the pus-saturated dressings. Two and often three times daily he had to renew these dressings, each change attended by great suffering and exhaustion. I vividly recall our painful disappointment on witnessing the gradual failure of the vital powers of patients with such an outflow of pus. Daily the visiting surgeon examined the pus to see if it was not becoming "laudable" and pressed iron tonics, but the final result was general infection.

From the time of Hippocrates there were two schools of surgeons based on the question of the treatment of wounds with and without pus. Although pus was almost universally present in healing wounds, still there were occasional instances where the wound healed without any discharge, but remained dry throughout the process. This incident gave rise to two methods of treatment, the "dry" and the "wet," the former being our healing by "first intention," and the latter by supuration or granulation (second intention). Though the intuitive genius of Hippocrates led him to teach healing by the "first intention," as the correct practice, he was violently opposed in the schools of Greece, and the "wet" treatment prevailed, its advocates regarding it important even to apply irritating dressings when pus was not freely secreted. These two schools continued to our time, the "wet" method being generally taught in the colleges and practised in the hospitals. Pus was not regarded as injurious to the wound except when of unhealthy quality and it was the quality, not the quantity, that interested the surgeon. Good pus was thick like cream and was called "laudable pus"; it was thought to indicate healthy healing. Practically we had a continuation of the old controversy of the healing of wounds by "first intention," the "dry method," or by supuration, the "wet method."

Lister's series of experiments by which he demonstrated the element in pus which renders it prejudicial to the healing of wounds, and the discovery of an effective remedy by which that element can be rendered inert from the moment of operation, are the most brilliant in the annals of science. Impressed with the fact that he had a mortality of 45 per cent in his cases of amputation, though great care was exercised to protect the wound, his mind recalled Pasteur's theory that microorganisms are the cause of putrefaction and that in his observations putrefaction was present only when there was supuration. He at once began experiments to test the truth of the theory of Pasteur by employing such agencies as he could command to destroy any germs present and still not harm the wound. He was finally led to the use of carbolic acid which proved satisfactory.

Lister began his experiments in 1865 and printed his first paper entitled, "On the Antiseptic Principle in the Practice of Surgery," in 1867. No one but a contemporary of that period can realize the storm of criticism and ridicule which greeted the author of that paper. He was accused of not being original in his work; of not obtaining better results than the old method of practice; of rendering operations tedious; of employing childish and ridiculous apparatus and dressings.

Lister answered his critics by the performance of new and more incredible operations without pus or fever and in the meantime improved the details. His reported excision of a knee-joint, 1878, and wiring a fractured patella, 1883, without supuration, brought to a climax the amazement of older surgeons at his pretensions. But what appealed to the elders as recklessness inspired the juniors with a commendable desire to test the truth of his statements in actual practice. I introduced the practice into the wards of Bellevue Hospital greatly

to the disgust of many of my colleagues who refused even to visit the wards where the patients were under treatment. I had the satisfaction, however, of a visit of Mr. Lister himself, while on a tour in this country, who generously commended my work and in his autobiography gives me the credit of introducing asepsis.

On visiting Lord Lister at his London residence in 1894, I found him quite pessimistic as to the then state of asepsis. He remarked that he believed true asepsis was rarely practised. "Why," he said, "I was in Berlin a few days ago and at the urgent request of friends attended the clinic of a noted aseptic surgeon. All his methods were excellent but on becoming confused in the operation he stopped, scratched his head, and completed the operation without sterilizing his fingers. That was an infected wound and its supuration will be attributed to the failure of asepsis."

On relating this incident to a former house surgeon to Lister's ward while he was experimenting with different agents, he said: "Lister was very much subject to perspiration especially when intently engaged in an operation, and I have often seen the sweat of his face fall into the wound without attracting his attention." Lister's great success, even under such unfavorable conditions, depended, probably, upon the thoroughness with which he finally applied disinfectants, for he dwelt especially upon that feature of aseptic treatment.

ANESTHESIA AND ASEPSIS

1867

With the introduction of asepsis into practice the art, operative medicine, became a true science. The entire process was governed by rules which ensured success. Compare Lister's statement that his best results in amputations showed a mortality of 45 per cent in 1864-1866 by the best methods then in use, with a recent report of a hospital in New York that in fifty consecutive cases of laparotomy, involving many varieties of intra-abdominal affection, 100 per cent of the patients made a good recovery.

It was very gratifying to me to learn of the following incident which occurred at the Bellevue Hospital recently where pus reigned supreme prior to 1867. A professor in one of the medical schools wished to exhibit a specimen of fresh pus to his class and naturally directed the messenger to apply at Bellevue Hospital. On making his errand known he was informed that pus in operation wounds had long since disappeared from the wards. Prior to the year 1867 healing by first intention in that hospital was neither expected nor sought by the surgeons. One of the most distinguished operators merely brought the surfaces of the wound together with adhesive strips and placed the wound in such a position that the pus would flow into a vessel, thus avoiding the necessity of frequent renewal of the dressings.

Now all is changed. Healing by first intention is always sought and the presence of pus in operation wounds is a severe reflection upon the care and skill of the staff in charge. But perhaps the greatest and most beneficial result of the im-

proved methods of treatment in operative surgery in this anæsthetic-aseptic era is the rapid convalescence of patients. The operation which formerly was the beginning of the end, owing to the exhaustion due to the suppuration which ensued, is now the beginning of a rapid convalescence. The feeble, nervous sufferer whose heart nearly ceased its action on the thought of an operation now approaches the operating room with a firm step, a normal pulse, and mounts the table with a smile. As operations under the old-time system were illustrated by the description of concrete cases, the vast improvement effected by the combined methods of anæsthesia and asepsis will be most thoroughly appreciated by a similar report of cases treated according to the principles established by these great epochs.

A young woman, aged 18, had suffered from a suppurative disease of the knee-joint five years, and was reduced in vitality to a helpless state. Her fear of an operation rendered her nervous system so sensitive that she had attacks of fainting when an operation was mentioned in her presence. And yet delay of an operation seemed more dangerous than its possible fatal results. A medical friend suggested the preparation for the operation be made in an adjoining room and he would visit her as chaplain and induce her to inhale chloroform to unconsciousness when she could be quietly removed to the operating table.

The ruse worked admirably. The patient was delighted with the perfumery, as the physician called it, and required but three or four inhalations to become insensible. Excision was performed, requiring an hour to complete it and its aseptic dressings, but her pulse continued good under the influence of hypodermic injections of heart stimulants. For several days she was in ignorance of the operation and was surprised that she had no longer pain in the knee but occasionally in her toes. One morning she saw a spot of blood on the sheet over the knee and was greatly alarmed as she had been told there was danger of fatal hemorrhage. On being assured that there was no danger and that the operation had been performed and she was recovering, she became frantic with joy. A vigorous appetite now developed and with freedom from pain and refreshing sleep, her rapid recovery was daily noticeable. The first dressing made was on the twenty-ninth day and there was only slight yellow staining but no pus. She had gained eight pounds in weight.

The following incident led me to adopt a method of anæsthetizing very feeble patients which has proved very serviceable. I was aiding a colleague in an operation for cancer of the breast on an old lady who was very fat, with a feeble intermittent pulse and nervous excitement. She had been prepared in the usual way with purgatives and simple diet. She had taken but little ether when her face became purple, her pulse disappeared and after a struggle to restore her she was pronounced dead.

It happened that I had a duplicate of this case on which I was to operate on the following day. I was so shocked by this experience that I delayed the operation and studied the

situation. The result was the conclusion that probably these patients' feeble and intermittent heart-action was due to over-laying and interstitial fat and required supporting rather than the depressing treatment then employed. Though this indication could be met by hypodermic heart stimulants I recalled two facts that determined my course, *viz.*: (1) Larrey, in his memoirs of the Napoleonic wars advised operations on soldiers while they are drunk, for they neither fear nor feel pain, and (2) hot milk is a quick nutrient and sustains a weak heart. Here were the remedial agents which my patient required to prevent fatal collapse.

After preparatory treatment I directed that at 8 o'clock on the day of the operation which was at 3 o'clock, the patient should receive one ounce of hot whiskey in a glass of hot milk, and the same must be repeated at 10 and 12 o'clock unless she was much disturbed. On visiting my patient at three o'clock on the day of the operation I found her in a most satisfactory condition. She had not required the stimulant the third time, having become quite excited about the details of the operation which had taken fantastic forms in her enlivened but disordered imagination.

On entering the ward she greeted me with some affectionate terms, expressed her delight that the operation was about to be performed and wished she could see the medical students present. Her face was flushed, eyes suffused, skin warm and her pulse full and regular at ninety-six. She came under the influence of the anæsthetic without a struggle and required an amount estimated at one-tenth that ordinarily given, the whiskey having already secured partial anæsthesia as Larrey suggested when he ordered wounded soldiers to be operated on while drunk. The pulse remained at ninety-six during the time occupied by the operation and the application of the aseptic dressings. She made an unusually rapid recovery, the pulse continued at ninety-six for several days; her appetite became vigorous; her happiness that the operation was over was extreme. But one dressing was employed and when it was removed there was no sign of pus and only the yellow staining of serum.

During the many years that I have used this anæsthetic, hot milk and whiskey, I have not seen a patient fear an operation, nor suffer from shock or collapse.

I trust these desultory reminiscences of the introduction of the two greatest epochs in human history may lead us to a proper appreciation of the labors, trials and skill of the surgeons of the pre-anæsthetic period, who amid the heart-breaking screams and uncontrollable struggles of patients devised and successfully performed the great operations which adorn the annals of surgery.

There is a profound truth in the remark of the historian, that "such knowledge widens the horizon, for a glance into the past, and an insight into the present of human activity, deepens the view for a comprehension of the ideas which guided the earlier and more recent physicians, and gives on the other hand to our daily professional labor a high consecration."

NOTES ON THE GROUP OF SYMPTOMS DESIGNATED AS EFFORT SYNDROME

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A little less than three years ago, when the stage was being set for the comedy entitled "The Second Mexican War," the writer was called into military service and assigned to the duty of physically examining the Maryland militia before its federalization. It was his first experience in the examination of large numbers of men and several interesting lessons were forthcoming which were later to prove most valuable. In the first place, an opportunity was afforded to appreciate the wide range of what may fairly be called the norm of the cardiovascular system. The prevalence of apical and conus systolic murmurs, the presence of short, scratchy, systolic murmurs near the sternum, the intensity of the second sounds at the base of the heart and their relation to age, third sounds, presystolic sounds, sharp clicks heard only in systole near the apex of the heart, the relation of posture to the position of the apex—all, with many other variations, are subjects well worth individual discussion, which may be dismissed here with the remark that for a proper valuation of such findings a competent knowledge of the normal is indispensable. Secondly, the variation in the pulse-rates of healthy individuals was noteworthy, and the dependence of this rate upon the condition of the mind and body was emphasized. Thus, tachycardia might be found in certain healthy young men who, having been told by a physician that they had heart trouble, did not believe they could pass the examination; or, again, men suffering from venereal infection and fearing its discovery might show an increased pulse-rate. Confirmed neurasthenics, a few men who had been forced into service by the jibes of their friends, those who were doubtful of their right to expose dependents to the charity of the world, any of these soldiers might appear for examination with a rapid heart. The association of certain organic physical diseases generally of an infectious character with tachycardia was constantly exemplified in the men with early or outspoken tuberculosis, bronchitis, or even with furunculosis.

A mental note was made of the high percentage of infected gums and carious teeth among the otherwise healthy and well-developed farmers, while the underdevelopment of the clerk group of the fifty men was conspicuous. One company having been recently organized in the vicinity of the mobilization camp was still below the numerical standard, and on the day before the examination, its officers, dependent for their positions upon the acceptance of the company by the army, collected a lot of young boys to supply the deficit. These lads claimed 18 years, but many of them were evidently younger.

During the three weeks of my duty at this camp, quite a number of men appeared at the hospital for re-examination because they were unable to perform their daily tasks. Many were young boys, a bit shaky, a little short of breath, with

acro-cyanosis of the extremities, sweating freely, and often complaining of sharp pains which they localized in the precordial region. A second physical examination, less hurried, disclosed nothing further of importance and it seemed that one was witnessing the attempt of a youth to do a man's work and the subsequent natural exhaustion. At the same time, others, many of whom had been noted as underdeveloped on the first examination, returned with similar complaints—they also had given out.

The rest of the summer was spent at the Artillery School at Tobyhanna where the Yale batteries and a few national guard organizations were training. During this period a few men were brought up for examination because they had not been able to stand the hard work—they had become irritable, did not get along with their fellows, and had lost weight. During the examination, they were apt to be a little shaky, the perspiration would roll down from their arm-pits, although the weather was comfortably cool; some degree of tachycardia was generally noted, and in response to slight exercise the rate would become excessive. Some of the soldiers had, in the course of the summer, slight attacks of tonsillitis or average colds of a few days' duration. It was interesting to follow these men. Whereas some of them went back to duty after a few days in the hospital and soon forgot their illness, others would remain below par for several weeks and have difficulty in doing the work that had caused them no discomfort before they had become sick. A few men showed a sensitive vagosympathetic balance, and were apt to faint in the ranks during a protracted muster. The different vaccinations were administered at this camp, and it was not infrequent to have in line husky, strong soldiers who were obviously afraid—the skin cold and clammy, with rapid heart and panting respiration. Others, blatantly brave, would faint from the prick of the needle.

The result of the summer's work was an appreciation of the infinite variations that are to be found among individuals—the variation in the sensitiveness of their reflex arcs, the variations in their bodily and mental reaction to physical and psychical trauma and so forth. Indeed each individual is so different in his bodily make-up and in his reaction to outside stimuli that the normal is very difficult to delineate and standardization becomes practically impossible.

Some of you have taken part in athletics at college, and will recall personal experiences similar to those that the writer himself remembers. Often, immediately before a football game or his race in a track meet, he suffered what now sometimes comes back in the form of a nightmare. Although, in excellent physical condition, he would go out on the field all a-tremble, with his heart racing and trying to beat its way through the chest, breath short and insufficient because of

a suffocative band that seemed to constrict the lower thorax and to prevent the ingress of air. Occasionally, after some particularly inspiring speech from a well-wishing alumnus, he would go out sweating profusely, with involuntary micturition, and even crying. The actual start of the game was always sufficient to bring back the normal functioning of the body. Again, you may remember your own condition or have seen others at the end of a short period of extreme bodily exertion, as at the end of a hard race for a quarter of a mile. Some men become pale with slight bluing of the mucous membranes, the cheeks sunken, trembling, occasionally fainting; others quite purple with puffed cheeks, watery eyes, nauseated even to vomiting, and often with blood-tinged sputum—both groups representing the signs of acute fatigue, the result of extreme exertion.

How often in the course of a wearing season does the coach tell one of his men that he is overtrained! The man is irritable, has lost weight, is not sleeping, his pulse-rate is sensitive to slight exertion, he is constantly sweating in cool weather, his general physical strength is decreasing, and he cannot approach his average record; while his team-mates are doing well and are improving under exactly the same work. Rest and a change of scene may soon return the overtrained man to his former condition, but the trainer has been to blame for the loss of time; he was treating all his athletes according to one standard, and this cannot be done with success. It is generally known that the captain of an athletic team is rarely so good during his tenure of office as he was the season before when he did not have to worry about the condition of the whole team in addition to performing his own individual work. It may even become necessary to send such a man away to continue his training by himself.

Experience in the training of track men develops the opinion that there are two outspoken types of athletes with numberless gradations between, the one capable of supreme concentration of energy for a short period of time, the dash man, the other slow-going and very resistant to fatigue; the former nervous, high strung, the hyperthyroid type, the latter steady and plodding, a successful long-distance runner. The training of the two groups should be quite different. The training of the sensitive dash man is always difficult. His work reflects his mental attitude, and the worry of a failure in recitations will be recorded by the reduction in his speed, whereas the phlegmatic distance runner plods along comparatively uninfluenced by his surroundings. Reverse these men, and the long-distance man is a failure in the sprints and the dash man will not only be unsuccessful in his new work but may also develop typical signs of *effort syndrome*.

One more observation from the field of athletics. Perhaps some of you have gone back some time after you left college, and have been asked by some enthusiastic coach to change your clothes and line up on the scrubs or to take out the hurdlers and show them some of the fine points of that race. All of us hate to admit that we are getting old, and perchance you have tried to do what you could. Just one such attempt may teach you the symptoms of effort syndrome and, in that event, you become

very sympathetic towards individuals suffering with this condition. The writer attempted such work within a few years of active athletic participation, at a time when he was in fair condition from tennis playing. Pride kept him from acknowledging failure before the crowd, and he kept up his unusual exercise for an hour or so; but for days afterwards he felt the effects—not only stiffness, but shortness of breath, untoward pulse acceleration, trembling, and precordial pain on slight exertion.

The same general reaction may be experienced during convalescence from even a slight infection. Those of you who have had influenza appreciate the long period that may elapse before you can comfortably perform your daily tasks. A physical examination may reveal no abnormality, but short walks are very tiring, and any continued mental labor is exhausting. Protracted asthenia after tonsillitis or slight colds is not infrequent in the medical dispensary.

It is an interesting fact, in this condition, that, bar an untoward accident such as an embolus or a ruptured valve, athletes or patients convalescent from acute disease never die during the period of activity. The will-power of individuals varies, and some men endure discomfort and withstand bodily punishment to a greater degree than others, but the limit in every case is always short of complete exhaustion of any organ of the body. This fact is intimately associated with some sort of protective mechanism of which the nervous system plays an important part and in which the resulting physical signs are manifested to different degrees as well as in different ways.

These observations serve as examples of conditions in which the symptom-complex called *effort syndrome* may obtain. Suggestions are made which point to a similarity of these signs to those manifested by the body in fear and in acute exhaustion.

In June of 1917, the writer was sent with The Johns Hopkins Unit to France where he was stationed for eight months in a base hospital. Here several facts were generally appreciated. The preliminary physical examination of the early recruits had been unsatisfactory, and for a while many of the patients were men who should never have been admitted to the service. There were not a few examples of dementia præcox, constitutional inferiority, grave neurasthenia, besides organic physical diseases. Many of these men showed, in addition to the signs peculiar to the individual organic disease, symptoms comparable to those already described. Then there were soldiers who had had no previous training, and who broke down under the strenuous physical demands which were especially exacting in the face of the poor housing facilities and unsatisfactory hygienic surroundings. There were cases of tuberculosis, infectious arthritis, horrible teeth, old infected tonsils, and similar chronic infections, and many of these men showed the same excessive reaction to exercise. Many soldiers who had come to base hospitals with acute diseases such as pneumonia, acute bronchitis, or acute tonsillitis and who had been discharged apparently well, had returned to the hospital with symptoms of fatigue on slight exertion. These symptoms were very apt to be referred by the battalion medical officers to the cardiovascular system because of the rapid heart or the shortness of breath. Moreover, the lack of knowledge on the part of

many medical officers of the range of the findings in the normal heart, caused, in face of symptoms so commonly associated with cardiac disease, a pathological interpretation of *conus* murmurs or third sounds, and the patient would be told that he had heart disease. After the occasional man suffering from organic disease had been weeded out and disposed of, and the better diagnosis of effort syndrome made, it was found that there was no satisfactory arrangement for the treatment or disposition of such patients. As the demand for acute beds increased, some of them would be sent back to duty, while others would be transferred to other base hospitals where they would lie around for a few weeks and then again be put on the active list. Or they might again be regarded as sufferers from organic heart disease, be put to bed and given digitalis. After this treatment, they would generally get out again with their symptoms made worse, which more than ever convinced the patients that they were suffering from heart trouble which could not be cured. Such a belief always militated against the patient being willing to take active exercise.

When the medical consulting staff was established under General W. S. Thayer, an effort was made to rectify this unfortunate condition and thereby avoid the resulting vicious circle in transportation, as a consequence of which these soldiers were spending most of their time in transit to and from the front line. Convalescent camps were to be established where treatment could be carried on intelligently, and where more protracted study of these patients might be made. At this time the writer was sent to England where he was attached to the British Military Heart Hospital which was doing excellent work under the direction of Dr. Thomas Lewis. Here were to be found the most extreme types of effort syndrome listed under the British medical nomenclature—disordered action of the heart. Dr. Lewis's work was fundamental. He showed that graduated exercises furnished a method for the functional testing of individuals and their subsequent classification for different degrees of physical work. This treatment, furthermore, proved to have an important curative value, so that he sent many of his patients back to front-line duty. The British medical corps was unfortunate in not having a psychiatric division, and, indeed, there was no special hospital in England for the treatment of psychoneuroses. A patient was either demented, whereupon he was sent to an insane asylum, or he was mentally correct. Such treatment as could be accorded the functional mental disorders was, as a rule, only that found in any base hospital conducted by a busy staff which must first meet the demands of the acutely ill. The treatment for the psychoneurotics was just the same as for the cases of effort syndrome, but this lack of differentiation furnishes one of the explanations of the high percentages of D. A. H. cases among the British. Dr. Lewis was preaching the gospel throughout England that these patients were made worse by being put to bed and being given digitalis; but it was slow work, and the general lack of knowledge as to what physical signs of the cardio-vascular system could be classified under the normal was a great handicap to overcome. Moreover, England was short of man power; underdeveloped men had to be

used for front-line duty, convalescence from acute infections was apt to be too short, and underaged as well as overaged men were constantly exposed to the demands of campaigning. Again, his hospital was well away from the firing line, and, as a result, his patients had passed through a series of base hospitals before he saw them, and by that time they had become thoroughly convinced, from their diagnosis cards and from information obtained from different medical officers, that they had definite heart trouble, which, to their minds, was incurable. Certainly the subjective symptoms strengthened that conception, and, moreover, four years of warfare had deprived some of them of any excess enthusiasm for staying in the army if there were any fair way of getting out.

Dr. Lewis and his staff had made many careful studies of their patients.¹ Controlled pharmaco-dynamic tests were employed with the following results: Atropin showed no difference between patient and control. Apocodeine generally gave a greater pulse-rate rise and there was a more marked cutaneous reaction in the patient group. Amyl nitrite had the same result. Pilocarpin produced more marked reaction among the patients. Digitalis had no more power to control the pulse-rate of the patients than of the controls, and the subjective symptoms were uninfluenced. Adrenalin, on the other hand, showed that the patients had a definite susceptibility to this drug so far as subjective symptoms go, but the rise in pulse-rate and blood pressure was about the same in the two groups. Another interesting study showed that the patients were apt to require a longer period after measured exercise before their pulse-rate lost its increase—five minutes, often, as compared to two minutes in the average control. X-rays and electrocardiograms showed no essential difference in the two groups. All in all, the work suggested that the disorder had to do with the peripheral nerves rather than with the central nervous system, and there seemed to be a hypersensitiveness of the sympathetic with no change in the vagal system.

After a stay of two months in England, the writer was sent back to France and assigned to duty at Convalescent Camp Number Two. This camp was the convalescent section for a large base hospital group, and had a capacity of 2000 patients. The work was very active and, at first, was complicated by the considerable amount of organization that was to be expected in the establishment of a new system. Graduated exercises were instituted under military discipline, so that each patient was tested as to his capacity for work and was not discharged to front-line duty unless he was able to perform comparable work. Each patient was carefully studied during his stay and any indicated laboratory tests were made. Moreover, a follow-up system was instituted which enabled us to arrive at definite conclusions about the method of treatment, and controlled the results.

The writer has summarized the first 5000 case-histories, and some of the findings have a direct bearing on the discussion of effort syndrome. Ninety-one per cent of all patients were sent back to full duty, and 3 per cent were returned to base hospitals for operation or for treatment which would probably later

admit their discharge in Class A. About $1\frac{1}{2}$ per cent of all cases were reclassified with the diagnosis of effort syndrome. This group was made up in equal proportions from patients with varying diagnoses on admission. That is, the effort syndrome cases were found just as frequently among patients who had had influenza or pneumonia, as among those who had been gassed. Every patient was especially studied for symptoms of hyperthyroidism. Only three cases of exophthalmic goitre were found among the 5000 under discussion, and, outside of these, only an occasional soldier showed struma, adenoma, diarrhoea, or any eye signs beyond a slight von Graefe. Nearly all the effort syndrome group showed a slightly accelerated pulse-rate, excessive sweating, restlessness, and dermatographia. Further signs that might be ascribed to hyperthyroidism were not conspicuous among these men.

The majority of patients on admission, especially those who had been suffering from an acute infection, showed what might be called effort syndrome. But these signs, in most instances, disappeared after treatment, and rarely reappeared after the patient's return to duty. In this connection it is interesting to compare the duration of the patients' stay in hospital before and after the establishment of convalescent camps. The functional test afforded by graduated exercises proved that, in general, the period which had been allowed in base hospitals for convalescence was too short. The average case of pneumonia needed eight weeks instead of the five permitted before discharge; mumps required 39 days instead of 18; herniotomies seven weeks instead of three and a half, and so forth. In all probability it was to this prolongation of the period allowed for convalescence that such favorable reports from the "follow up" system were due.²

Of these 5000 cases the diagnosis of anxiety neurosis was made in 192. It would lead far afield to enter into a discussion of this disorder and its relation to fear; however, many of these patients showed symptoms quite similar to those of effort syndrome. The recovery of these soldiers was very slow, necessitating, on an average, seven weeks. They needed much more individual care than did the general run of patients, and the success of the treatment depended, in large part, upon the ability of the individual ward doctors to handle psychoneurotics. A good many of them certainly had a psychasthenic basis, or at least had a weakened will-power. But there, again, the extremes of normal are hard to mark out, and, moreover, the degree of psychic shock had been extremely variable. One hundred and sixty or 43 per cent were sent back to front-line duty and 4 per cent were returned to the base hospitals for operations or because the patients had contracted some acute infection. That is, 13 per cent were reclassified as compared with the general percentage for the 5000 cases of 6 per cent reclassified. On discharge many of these reclassified men showed symptoms of effort syndrome in varying degrees. Of the 80 patients admitted with the diagnosis of exhaustion, 95 per cent were sent back to the front lines. They had required an average of six weeks in the hospitals and camp, but after recovery they "carried on" normally in their original commands. Many of this group had shown signs of effort syndrome on admission.

Not far from our camp was a hospital devoted entirely to the treatment of war psychoses. As a result of exchange visits, the physicians of both places learned to appreciate the similarity of the symptoms to be found in both establishments. In many instances we agreed that the original diagnosis had depended in large part upon the specialty of the physician who had first seen the case—the psychiatrist favoring the diagnosis of anxiety neurosis, the cardio-vascular man, effort syndrome. At first the psychiatrists had claimed, and probably correctly, that their specialty was fundamentally concerned, but they became less insistent that such patients should be sent to their hospital when they came to appreciate that we all were treating these soldiers in much the same way. Indeed, after the armistice, when the psychiatrist in charge had issued an order that no cases of war psychoses should be sent to the states, and when the disposition of these patients became a problem, the psychiatrists began to unload on us and we received numerous soldiers from their hospital with the combination diagnosis of (1) effort syndrome; (2) anxiety neurosis. We rather felt that this order of diagnosis should have been reversed, but such a change would have only started a vicious circle of transportation which, of course, would have been foolish. It seems fair, then, to assert that individuals vary as to their power of resistance to psychic trauma, and that many individuals after prolonged psychic trauma may show signs of effort syndrome.

With this accumulated information, it is interesting to speculate as to the cause of effort syndrome. Many investigators believe that these patients are suffering from a definite disease, and are endeavoring to find a single etiological basis. Probably such efforts will never be successful, and it seems rather that effort syndrome is a name for a medical wastebasket whose contents must be carefully sorted into etiological groups. Some of these groups are very easily understood—those with a definite physical basis. Under this caption appear convalescents, both those from recent acute infections and those whose original period of convalescence was so short that they were subsequently returned to the hospital for continued treatment. Effort syndrome after exhaustion seems reasonable, as does that in association with actual physical disease—tuberculosis, tonsillitis, exophthalmic goitre, and so forth. Another sample is furnished by hyperthyroidism where, in addition to the symptoms of effort syndrome, there should be further signs incriminating the thyroid—diarrhoea, struma, adenoma.

It is possible to conceive of psychical conditions which may induce the symptoms of effort syndrome. Acute fear gives such symptoms; patients who are constitutionally inferior, those exposed to prolonged psychic trauma, perhaps another group—individuals the victims of chronic fear—all of these patients might be regarded as supplying an etiological basis fairly well understood. It is certainly true that men, who had been on the front-line for a year with no discomfort, might receive a culminating psychic shock that would induce the onset of their symptoms.

There are, however, many cases which are not so easily understood, and do not seem to belong to any of these different etiological groups. It is possible that we are here dealing with

the training of track men on a large scale. Just as putting all athletes to running long distances will develop the symptoms of effort syndrome, so submitting large numbers of young men to the protracted training of a recruit, where individuality is entirely disregarded, will show a number of men who give out. The phlegmatic distance man and the nervous dash man are fundamentally different people, with different bodily make-ups. The gradations between the two extremes are limitless.

To designate diseases, names are employed. These names describe maladies which are different, with different etiology, different pathology and different courses. If this view as to the multiplicity of etiological factors is conceded, then effort syndrome is no more a correct diagnosis than is jaundice or tachycardia. To all the names for this condition, which, by the way, have been applied by cardio-vascular specialists rather than by internists, to these names—irritable heart, disordered action of the heart, neuro-circulatory asthenia, effort syndrome—it would be foolish to add others. But it does seem worth while to endeavor to go back of a prominent symptom and to attempt a primary diagnosis, and allow the symptom-group to be secondary. At our camp, where we all believed in the multiplicity of causes, such effort was made, and more and more we employed such combination diagnoses as the following: Protracted convalescence, effort syndrome; exhaustion, effort syndrome; psychasthenia, effort syndrome; anxiety neurosis, effort syndrome, and so forth. It is this reason which prompted the choice of a title for these notes, not effort syndrome, but the group of symptoms designated as effort syndrome.

Just a word as to the pathological physiology of this condition.

What is the actual construction of this protective mechanism? It is not yet evident. Perhaps explanations will be forthcoming some day from the physiologists. The processes involved in effort syndrome may well be related to those in fatigue or fear. Barcroft has shown that patients with effort syndrome are not benefited by the oxygen chamber—a treatment with the purpose of oxidizing any fatigue products that may have been accumulated in the body. Nor have we, as yet, any proof that, as in fatigue, there are definite chemical substances concerned. Other studies suggest that the endocrine glands play a part, and different hypotheses have been evolved on this basis. Dr. Cannon's conception of the mechanism of fear—"an adrenalinemia due to nervous stimulation of the adrenal glands"—is most attractive, and it is very unfortunate for our peace of mind that his hypothesis has not been substantiated by the work of other investigators. In this connection it is important to remember that, while exhaustion in some way is brought about by the accumulation of metabolic products together with a depletion of energy producing substances, the initial action of these same substances is distinctly physiological and provides an increased capacity of the body for work. The demarcation between the helpful and the harmful is not sharp. In the same way, it is not at all impossible that the symptoms of effort syndrome are the result of a perversion or an overaction of a normal bodily mechanism.

It is hardly worth while to enter into a discussion of the thyroid and its relationship to effort syndrome. It is all too speculative. But it is a fact that nearly everyone has started out in their work with these patients with the idea that the thyroid was etiologically concerned. Excluding the definite cases of exophthalmic goitre and cases of hyperthyroidism with actual localizing symptoms, it may well be that the thyroid is concerned with the production of some of the symptoms of effort syndrome, but there is no investigation yet forthcoming that has proved it to be fundamental. Treatment, directed to this special organ, would be symptomatic treatment, and, in a way, would be comparable to the extirpation of the liver in cases of pneumonia that show jaundice. The jaundice, in great part, would be cured, but there would be no improvement in the pneumonia.

While it may be that the importance of effort syndrome has been overestimated, and although it is possible that such a diagnosis is often a confession of failure on the part of the examining physician, the discussion is valuable. From it comes a conclusion which has been well expressed by DaCosta: "In bringing this inquiry to an end, I may be permitted to point out what I believe to be its chief interest and value. To the medical officer it may be of service as investigating a form of cardiac disorder which every severe or protracted campaign is sure to develop. And, from a military point of view, further, it enforces the lessons, how important it is not to send back soldiers, just convalescent from fevers or other acute maladies, too soon to active work. It suggests that their equipments be such as will not unnecessarily constrict, and thus retard or prevent recovery; that recruits, especially very young ones, be, so far as practicable, exercised and trained in marches and accustomed to fatigue before they are called upon to undergo the wear and tear of actual warfare, and it exhibits some of the dangers incident to the incessant and rapid maneuvering of troops. True, on a movement executed on the double quick may depend the issue of a battle; a forced march may determine the fate of a nation; and the time can never come when purely physical considerations can forbid either one or the other, or dictate how often they may be ordered. But every commander should be made aware that in so using his men he is rendering some unfit for further duty, impairing others, and thus be led to count the cost of the frequent use of such active movements as carefully as he would the holding of a particular part of a line or the assault on another." To this excellent summary, a few personal impressions might be added by way of conclusion.

1. The *effort syndrome* is not a disease entity, but signifies a variety of symptoms resulting from different etiological factors, among which constitutional variation in individuals should be emphasized.

2. Prophylaxis is important to consider and among helpful procedures to this end a sufficiently prolonged period of convalescence is pre-eminent.

3. All recruits as well as convalescents from medical and surgical conditions should be subjected to competent functional tests before they are sent to front-line duty. Graduated exercises afford such a method of examination, and act, more-

over, as a therapeutic procedure, besides offering a good basis for the reclassification of soldiers.

4. Physicians in their constant thought of the pathological are often not thoroughly appreciative of the normal findings of, especially, the cardio-vascular and nervous systems.

5. The effort syndrome represents findings of varying and often slight changes from the normal which are by no means confined to soldiers, but are to be found constantly in the clinic of every physician.

REFERENCES

1. Medical Research Committee (Dr. Thomas Lewis): Reports upon soldiers returned as cases of "Disordered action of the heart" or "Valvular disease of the heart."
2. Bridgman, E. W.: Notes on the duration of normal convalescence. Arch. Int. Med.—to be published.
3. Cannon, W. B.: Bodily changes in pain, hunger, fear, and rage. Appleton and Co., 1916.
4. DaCosta, J. M.: On irritable heart; a clinical study of a form of functional cardiac disorder and its consequences. Amer. Jour. Med. Sciences, 1871, LXI, 1.

NOTES ON NEW BOOKS

Quarterly Medical Clinics. A Series of Consecutive Clinical Demonstrations and Lectures. By FRANK SMITHIES, M.D. Vol. I, No. I. Cloth \$2.25, paper \$1.50. (St. Louis: Medicine and Surgery Publishing Company, 1919.)

A large group of physicians throughout the country, especially those located away from the main centers, have always felt keenly the difficulty of keeping in touch with up-to-date methods in clinical medicine. To meet this demand, during the last few years a number of publications have sprung up, devoted to the teaching of medicine by the method of case histories and clinics. It is with interest, therefore, that we read the latest offering in this direction—the Medical Clinics of Dr. Frank Smithies.

In criticizing a work of this sort, one should have clearly in mind the purpose for which it is intended—to aid the student and the general practitioner. As the writer himself states in the preface, much of the material is elementary and treated along simple lines; but, at the same time, we find in these clinics well presented cases, with concise summaries of modern views as to etiology and treatment, together with sections on the technique of diagnostic and therapeutic procedures. Fifteen cases are taken up in the first volume, which deals mainly with abdominal diseases but also with other conditions. The general plan is well illustrated by Case 5, an instance of pernicious anemia. The history, examination and study of the case are first presented, followed by a section on differential diagnosis, and a discussion of severe chronic anemias in general, with particular reference to the changes in the hematopoietic system. Next comes a section on treatment, with a discussion of methods of transfusion and of testing the compatibility of the donor's blood. Finally, certain laboratory methods are given in detail.

The book is attractively gotten up, the material is arranged in convenient form and there are numerous excellent illustrations and diagrams. The value of the material would be considerably enhanced by the addition of a brief index.

A. L. B.

Human Intestinal Protozoa in the Near East. By C. M. WENYON and F. W. O'CONNOR. (London: John Bale, Sons and Danielsson, 1917.)

This monograph of 210 pages represents a collection of four papers which appeared in the Journal of the Royal Army Medical Corps during the early months of 1917, to which has been added a fifth section made up of the clinical histories of patients studied and treated for intestinal protozoa. The authors have carried out an enormous amount of well-planned work, having studied almost 3000 cases, repeatedly examining many of the patients, and it is the result of this work that is reported. It is pleasing to note that their observations have confirmed almost all of the facts heretofore considered established in regard to protozoan infections of the intestine, and comforting to one with less experience that even these observers with such opportunities for studying the problem must still write, "It is often quite impossible to distinguish unencysted forms of *E. histolytica* from *E. coli*." Section IV

detailing experiments with flies as carriers is most interesting, indeed startling, and may well be calculated to discourage casual travel in the regions in which this work was done. For instance, of two hundred flies caught at random in different localities in Alexandria, in the droppings of fifteen was found one or more of the following: cysts of *E. histolytica*, *E. coli*, *Lambia intestinalis*, the oöcyst of a coccidium, and eggs of *Taenia saginata*, *Ankylostoma duodenale*, *Trichuris trichuria*, *Heterophyes*, and *Bilharzia*. In another section therapeutics is discussed and the results obtained are enlightening but rather discouraging. Two intestinal flagellates and an amoeba are described which the authors believe have not been described before.

This monograph is a definite contribution to the subject of intestinal protozoa. The authors have used a splendid opportunity to good advantage. The subject matter is well presented, it makes interesting reading, and there is a good index. F. A. E.

The Soldier's Heart and the Effort Syndrome. By THOMAS LEWIS. Cloth \$2.25. (London and New York: Shaw and Sons, Paul B. Hoeber, 1918.)

Dr. Lewis has been the leader in the recognition and treatment of that recently acknowledged relative of all disease—Effort Syndrome. At Hampstead and later at Colchester, he taught his rational and practical views of the handling of heart disease, a medical condition that accounted for 10 per cent of all discharges from the British army. This experience and advice he sums up in clear, straight-forward language in the present book, "primarily written with the intention of helping medical officers of recruiting, discharging and pensioning boards, and medical officers in charge of patients." It has, however, more than a military application, for it discusses the methods of physical examination of the cardio-vascular system from a somewhat novel view-point. Many times I have heard Dr. Lewis bewail time lost in insignificant discussions of some of the manifold variations of the text-book pictures of health or disease! Test the patient's ability to perform exercise, functionally try him out! The army could not use a healthy heart in a man constitutionally inferior, whereas a slightly diseased heart in an otherwise healthy body was utilisable. We physicians are apt to overlook this practical problem in civilian life, and many a patient is consigned to a life of invalidism because of a heart condition that has been recognized as not normal. The reserve power of the vascular system is enormous, and even a badly affected heart can be intelligently managed so as to satisfy the demands of a controlled life. Perhaps the greatest lesson in Dr. Lewis's book is a new approach to the old story that many variations make up the normal. It is rarely possible to diagnose disease by one finding, and there is a general tendency to ascribe too much importance to the presence of sounds that are not encompassed in the regulation "lub-dupp" of the text-book. Careful physicians may not follow Dr. Lewis in his statement that accurate delineation of the heart's size by percussion is not possible, but his valuation of test exercise is not too high and is well worth the careful thought of all medical men. E. W. B.

BOOKS RECEIVED

- United States, Navy Department, Bureau of Medicine and Surgery.* Annual Report of the Surgeon General, U. S. Navy Chief of the Bureau of Medicine and Surgery to the Secretary of the Navy for the Fiscal Year, 1918. 8°. 267 pages. Government Printing Office, Washington.
- United States, Department of Commerce, Bureau of the Census.* Census of the Virgin Islands of the United States, 1917. Prepared under the supervision of Eugene F. Hartley. 1918. 8°. 174 pages. Government Printing Office, Washington.
- American Gynecological Society.* Transactions, Vol. 43. For the year 1918. 8°. 480 pages. Wm. J. Dornan, Philadelphia.
- American Ophthalmological Society.* Transactions. Vol. XVI. 1918. 8°. 412 pages. American Ophthalmological Society, Philadelphia.
- A Century of Science in America.* With Special Reference to the American Journal of Science, 1818-1918. By Edward Salisbury Dana, Charles Schuchert, Herbert E. Gregory, Joseph Barrell, George Otis Smith, Richard Swann Lull, Louis V. Pirsson, William E. Ford, R. B. Sosman, Horace L. Wells, Harry W. Foote, Leigh Page, Wesley R. Coe, and George L. Goodale. 1918. 8°. 458 pages. Yale University Press, New Haven; Humphrey Milford, Oxford University Press, London.
- The Rockefeller Foundation.* Annual Report, 1917. 8°. 377 pages. New York City.
- Guy's Hospital Reports.* Edited by F. J. Steward, M.S. and Herbert French, M.D. Vol. LXIX being Vol. LIV of the Third Series. 1918. 8°. 276 pages. J. & A. Churchill, London.
- Quarterly Medical Clinics.* A Series of Consecutive Clinical Demonstrations and Lectures. By Frank Smithies, M.D. Vol. I, No. 1, January, 1919. 8°. 188 pages. Medicine and Surgery Publishing Company, Inc., Metropolitan Building, St. Louis.
- Public Health Reports.* Issued Weekly by the United States Public Health Service. Containing Information of the Current Prevalence of Disease, the Occurrence of Epidemics, Sanitary Legislation, and Related Subjects. Vol. 32, Part 2, Nos. 27-52, July-December, 1917. 8°. Government Printing Office, Washington, 1918.
- Rockefeller Institute for Medical Research.* Monograph No. 9. The Use of Blood Agar for the Study of Streptococci. By James Howard Brown. 1919. 4°. 122 pages. New York.
- Surgical Treatment.* A Practical Treatise on the Therapy of Surgical Diseases for the Use of Practitioners and Students of Surgery. By James Peter Warbasse, M.D. In three volumes, with 2400 illustrations. Vol. III. 1919. 8°. 861 pages. W. B. Saunders Company, Philadelphia and London.
- Complete Index to Volumes I, II, and III of Warbasse's Surgical Treatment.* 1919. 8°. 123 pages. W. B. Saunders Company, Philadelphia and London.
- Gilbertus Anglicus.* Medicine of the Thirteenth Century. By Henry E. Handerson, A.M.M.D. With a Biography of the Author. 1918. 8°. 77 pages. The Cleveland Medical Library Association, Cleveland, Ohio.
- Human Infection Carriers.* Their Significance, Recognition and Management. By Charles E. Simon, B.A., M.D. 1919. 8°. 250 pages. Lea & Febiger, Philadelphia and New York.
- Michigan State Board of Health.* Forty-sixth Annual Report of the Secretary of the State Board of Health of the State of Michigan for the Fiscal Year Ending June 30, 1918. 8°. 180 pages. Fort Wayne Printing Company, Fort Wayne, Indiana. 1919.
- Clinical Microscopy and Chemistry.* By F. A. McJunkin, M.A., M.D. Illustrated. 1919. 8°. 470 pages. W. B. Saunders Company, Philadelphia and London.
- Essentials of Surgery.* A Textbook of Surgery for Students and Graduate Nurses and for Those Interested in the Care of the Sick. By Archibald Leete McDonald, M.D. 46 illustrations. Lippincott's Nursing Manuals, 1919. 8°. 265 pages. J. B. Lippincott Company, Philadelphia and London.
- Tuberculosis of the Lymphatic System.* By Walter Bradford Metcalf, M.D. 1919. 8°. 216 pages. The Macmillan Company, New York.
- The Early Treatment of War Wounds.* By Colonel H. M. W. Gray. 1919. 8°. 299 pages. Henry Frowde; Hodder & Stoughton, London. Oxford University Press, American Branch, New York.
- Lice and Their Menace to Man.* By Lieut. L. L. Lloyd, R. A. M. C. (T.) With a chapter on Trench Fever. By Major W. Byam, R. A. M. C. 1919. 8°. 136 pages. Henry Frowde; Hodder & Stoughton, London. Oxford University Press, American Branch, New York.
- The Operative Treatment of Chronic Intestinal Stasis.* By Sir W. Arbuthnot Lane, Bart., C.B. Fourth edition revised and enlarged. 1918. 8°. 328 pages. Henry Frowde; Hodder & Stoughton, London. Oxford University Press, American Branch, New York.
- Surgical Clinics of Chicago.* Vol. 3, No. 1. With 75 illustrations. 1919. 8°. 236 pages. W. B. Saunders Company, Philadelphia and London.
- The Whole Truth About Alcohol.* By George Elliot Flint. With an Introduction by Dr. Abraham Jacobl. 1919. 12°. 294 pages. Macmillan Company, New York.
- Military Surgery of the Ear, Nose and Throat.* By Hanau W. Loeb, M.D. Medical War Manual No. 8. 1918. 24°. 176 pages. Lea & Febiger, Philadelphia and New York.
- Vegetative Neurology.* The Anatomy, Physiology, Pharmacodynamics and Pathology of the Sympathetic and Autonomic Nervous Systems. By Dr. Heinrich Higier. Authorized translation by Walter Max Kraus, A.M., M.D. Nervous and Mental Disease Monograph Series No. 27. 1919. 8°. 144 pages. Nervous and Mental Disease Publishing Co., New York and Washington.
- A Study of the Mental Life of the Child.* By Dr. H. Von Hug-Hellmuth. Translated from the German by James J. Putnam, M.D. and Mabel Stevens, B.S. Nervous and Mental Disease Monograph Series No. 29. 1919. 8°. 154 pages. Nervous and Mental Disease Publishing Company, Washington.
- The Anatomy of the Peripheral Nerves.* By A. Melville Paterson, M.D., F.R.C.S. 1919. 8°. 165 pages. Oxford Medical Publications. Henry Frowde; Hodder & Stoughton, London.
- Surgical Aspects of Typhoid and Paratyphoid Fevers.* Founded on the Hunterian Lecture for 1917—Amplified and Revised. By A. E. Webb-Johnson, D.S.O. With foreword by Lieut. General T. H. Goodwin, C.B., C.M.G., D.S.O. 1919. 8°. 190 pages. Henry Frowde; Hodder & Stoughton, London.
- A Text-Book of Biology.* For Students in General, Medical and Technical Courses. By William Martin Smallwood, Ph.D. (Harvard) Third edition, enlarged and thoroughly revised. Illustrated with 235 engravings and 8 plates in color and monochrome. 1918. 8°. 306 pages. Lea & Febiger, Philadelphia and New York.

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DR. HOWARD A. KELLY

PROFESSOR OF GYNECOLOGY IN THE JOHNS HOPKINS UNIVERSITY AND GYNECOLOGIST-IN-CHIEF TO THE JOHNS HOPKINS HOSPITAL

By THOMAS S. CULLEN

Howard Atwood Kelly was born in Camden, New Jersey, on February 20, 1858. He received his bachelor's degree at the University of Pennsylvania in 1877 and graduated in medicine from the same university in 1882. He settled in Philadelphia and early attracted attention by his marked success in handling cases then before supposed to be inoperable.

During the year 1882-83 Dr. Kelly, while a resident physician in the Episcopal Hospital, built up a remarkably good gynecological dispensary clinic, demonstrating what might be accomplished by paying especial attention to this group of hitherto much neglected cases. After his internship was completed he began practice in an office on West Front Street in Philadelphia, and established a modest hospital on D Street consisting of two rooms on the second floor of a two-story house; Mrs. Wood, the wife of a working-man, taking care of the patients.

In 1884 the young surgeon removed his hospital to a three-story house on Cumberland Street, and a year and a half later to Norris Square to a four-story house on Diamond Street. Here the new hospital grew rapidly and became the Kensington Hospital. Established in 1883, it was incorporated in 1887, and has been supported by voluntary contributions. At this period Dr. Kelly took up his residence on Hancock Street across the square from the hospital.

Dr. Kelly has always been an indefatigable worker and his early labors in Philadelphia, especially in the Kensington

Hospital, are vividly remembered to this day. Thus, when an important post became vacant in the University of Pennsylvania and several men were being considered for the position, Dr. Osler, when asked whom he favored, replied, "I am backing the Kensington colt."¹ With his characteristic excellent judgment of men, he had picked out Dr. Kelly as a man of exceptional promise and it was little wonder that a short time later Kelly was called from the University of Pennsylvania to The Johns Hopkins Hospital to become its first professor of gynecology and obstetrics.

¹ Since the above was written the following note has been received by Dr. Hurd from Dr. Osler:

"The circumstances were these: Goodell had resigned, and there was no end of discussion as to who should take his place. On several occasions I had gone to Kensington to see Kelly operate, and I happened to mention to Pepper that I had never seen anybody do abdominal work with the same skill. He knew of Kelly, but had not, I believe, seen him operate, which he immediately arranged to do. Then one evening at the Biological Club, Horatio Wood and Mitchell were discussing Goodell's successor, and I said that Pepper and I were backing a dark horse—a Kensington colt. With that, Leidy chimed in with a remark that if it was young Howard Kelly, his former prosector, he would back him heartily. This is how I remember the story.

"How extraordinarily successful he has been! Only those of us who know the work as it was, realize how much the profession (and the public) owes to such men as Kelly."

Kelly went abroad for the first time in 1886, visiting England, Scotland and Germany. Among the well-known men whom he met were: Brennecke, in Magdeburg; Snger, in Leipzig; Schroeder and Martin, in Berlin; Fehling, in Basle; Hegar, in Freiburg; Koeberle, in Strasburg; and Berry Hart, in Edinburgh.

While in England Dr. Kelly attended the meeting of the British Medical Association at Brighton. Lawson Tait gave the address on surgery; his topic was gall-bladder surgery. Kelly was invited to take part in the proceedings of the gynecological section and reported a case in which he had diagnosed and removed an unruptured extra-uterine pregnancy. Tait, who at this period was studying extra-uterine cases, in discussion claimed that the diagnosis was a matter of "expert instinct" and therefore hardly attainable by the average man. Kelly in reply pointed out that in his case the signs were: a definite cessation of the menses, a small tumor to the right of the uterus, gradually increasing in size month by month and very tender, followed by a cessation of growth and a gradual shrinkage; at operation an unruptured right tubal pregnancy was found. Tait remarked that he did not concur in the "cock-sure diagnosis" of the young man and made light of his communication. Thus, early in his career, the future leader of American gynecology had an encounter with the then dominant figure in abdominal surgery in England.

In 1888 he again visited Europe, this time in company with Hunter Robb and Constantine Goodell. In Berlin he met Virchow, secured permission to work on cadavers in the Charit and spent much time in determining from an anatomical standpoint just how the ureters could best be catheterized. From Berlin the party went to Prague and saw Pawlik catheterize the ureters through the water-filled bladder.

In 1889 he returned to Germany on a still more important mission. On June 27, he was married to Letitia Bredow in the Danzig Cathedral.

In 1888 Dr. Kelly was appointed associate professor of obstetrics in the University of Pennsylvania and held this position until his departure for Baltimore, in 1889.

In 1889, at the age of 31, he entered upon his duties as professor of gynecology and obstetrics in The Johns Hopkins University and as gynecologist and obstetrician-in-chief to The Johns Hopkins Hospital. At that time The Johns Hopkins Medical School was still a thing of the future, but the hospital and pathological laboratory were already giving courses to a large number of medical men and surgeons who came to do postgraduate work.

In these early days Dr. Kelly's hospital work was limited exclusively to gynecology, for as yet no accommodations had been supplied for obstetrical cases. With the opening of the medical school in 1893 it became imperative to provide facilities for caring for obstetrical patients. This branch was gradually developed by the efforts of Dr. J. Whitridge Williams, and in 1899 the two important branches, gynecology and obstetrics, were separated and became independent departments. From then on Dr. Kelly concentrated all his endeavors to the develop-

ment of gynecology. Garrison terms Professor Kelly "a recognized leader of his science in America." He adds:

He was a pioneer in the use of cocaine anesthesia (1884), in the treatment of retroflexion of the uterus by suspension (1887), in the introduction of the operations of nephro-ureterectomy, nephro-ureterocystectomy, vertical bisection of the cervix for tumors and inflammation, and ideal appendectomy; the procedures of a roscopic examination of the bladder and catheterization of the ureters, exploration of the rectum and sigmoid flexure, diagnosis of ureteral and renal calculi by wax-tipped bougies, diagnosis of hydronephrosis by injection and measurement of the capacity of the renal pelvis, operation on the kidney by the superior lumbar triangle, treatment of malignant tumors by radium, and various improvements in the treatment of vesico-vaginal fistulae. He is the inventor of the Kelly pad, new rectal and vesical specula, and his *Operative Gynecology* (1898) and *Medical Gynecology* (1908), both illustrated with Max Br del's drawings, are full of improvements in the science which have made these books among the best American Treatises of the time.

He is also known by his valuable historical contributions on hypnotism, American gynecology, appendicitis, vesico-vaginal fistula, medical botanists, medical illustration, and American medical biography (1912). His "Stereo-Clinic" (1910-13) is a permanent photographic record of recent surgical procedures.

The tendency of recent gynecology to become merged into general abdominal surgery has been wittily signalized by Dr. Kelly as follows:

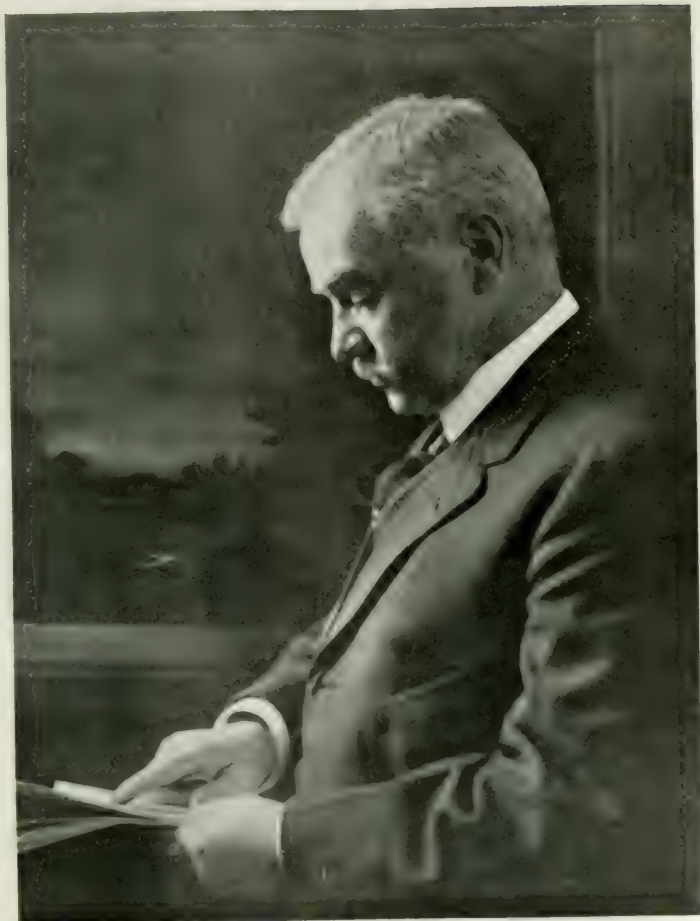
"The vital question which now affects gynecology is this: Is she destined to live a spinster all her days? For we see her on one hand courted by her obstetrical ancestor, who seeks to draw her once more into an unholy, unfruitful alliance, destined to rob her of virility, to be rocked into innocuous desuetude for the rest of her days' in the obstetric cradle, sucking the withered ancestral finger in the vain hope of nourishment (with apology for mixed metaphor). On the other hand, we see her wooed by a vigorous, manly suitor, General Surgery, seeking to allure her from her autonomy into his own house, under his own name, obliterating her identity."²

No one connected with The Johns Hopkins Hospital has written more or has added more to the knowledge of his department than has Dr. Kelly. A glance at his bibliography will give the reader a fair idea of the magnitude of his work. Here it is only possible to mention his more important papers. The first article from his pen was entitled "Some Rare and New Anomalies in Man; with Three Cases of Double Femoral Artery" (1882).

Among his subsequent papers we find "An Ovarian Cyst Weighing One Hundred and Sixteen Pounds Successfully Removed" (1885); "Hysterorrhaphy" (1886); "Extra-Uterine Pregnancy" (1886); "Asepsis Not Antiseptis" (1886); "Cæsarean Section" (1888); and "Palpation of the Ureters in the Female" (1888).

IN THE JOHNS HOPKINS HOSPITAL BULLETIN of January, 1890, appears his article on "Hysterorrhaphy." This operation was a marked improvement on the method hitherto employed to hold up the retroverted or retroflexed uterus, and remained in vogue for nearly 20 years, after which Dr. Kelly himself abandoned it for the improved method of shortening the round ligaments—a method which holds the uterus up equally well

² Garrison, *History of Medicine*, 2. ed., Phila., W. B. Saunders, 1917, 639-640.



DR. HOWARD A. KELLY.

Professor of Gynecology in The Johns Hopkins University and Gynecologist-in-Chief to The Johns Hopkins Hospital for thirty years—from the opening of the Hospital in 1889 to 1919.

and which is rarely, if ever, followed by difficulties at childbirth.

From his article "The Gynecological Operating Room in The Johns Hopkins Hospital, and the Antiseptic and Aseptic Rules in Force," published in 1890, we get a pleasant glimpse of the plan of procedure followed in the pioneer days of the hospital. One can hardly realize that at that time after nearly every abdominal operation a glass drainage-tube was used for several days and that each day this glass tube was not only pumped out with a syringe to which a rubber tube was attached, but once a day the tube was turned around in order that the omentum might not insinuate itself through the small holes in it and become fixed.

Dr. Kelly's interest in the ureteral work continued and in 1892 we find a paper entitled "My Recent Ureteral Work." In 1892 he devoted much time to the study of the bladder and ureter and in these investigations he was assisted by Albert L. Staveland, William W. Russell, Thomas S. Cullen and John G. Clark.

The BULLETIN for 1893 contains the results of his labors under the title "The Examination of the Female Bladder and the Catheterization of the Ureters under Direct Inspection." For years he had been catheterizing the ureters with varying success by palpation, or as he called it by the "fishing method." Dissatisfied, however, with this relatively blind method, he decided to put the patient in the knee-chest posture and introduce a tube into the bladder hoping that this viscus would balloon out as the vagina does when the speculum is introduced. This procedure succeeded admirably and he was able to see clearly not only the ureteral orifices, but also nearly all parts of the bladder. At once he grasped the possibilities of this method of studying the bladder and ureters in women and immediately developed and perfected the necessary instruments. This armamentarium was so complete that hardly another instrument, vesical or ureteral, has been added since. To Dr. Kelly alone belongs the credit of not only discovering, but also of working out in detail this fundamental and important method of gaining an insight into the secrets of the bladder, ureters and kidneys. The procedure has been adopted throughout the world.²

Profiting by his experience in distending the bladder with air when the patient was in the knee-chest posture, he applied the same principle to the inspection of the rectum, and finding the exposure equally good he had a series of proctoscopes made. These varied in length and caliber and enabled the surgeon to inspect the rectum and sigmoid for a distance of from eight to ten inches and to bring clearly into view pathological conditions that otherwise would have been overlooked. Proctologists agree that the Kelly method has aided them greatly in the study and treatment of diseases of the rectum.³

In no department of abdominal surgery has there been greater advance than in the handling of uterine myomata.

In the early days of the hospital it was customary to place a rubber ligature around the growth and then cut the tumor away. Sometimes the stump would slip through the rubber ligature and alarming hemorrhage would follow. Many surgeons must be credited with a share in simplifying the technique of removing the myomatous uterus, but Kelly's "left and right method" must be regarded as one of the most important advances in the simplification of such hysterectomy cases.⁴

IN THE JOHNS HOPKINS HOSPITAL BULLETIN of 1898 there appeared an article by Dr. Kelly entitled "The Catheterization of the Ureters in the Male through an Open Cystoscope with the Bladder Distended with Air by Posture." The cystoscope was similar to his female cystoscope, but a good deal longer. With this instrument the late Dr. James Brown, a pioneer urologist, demonstrated catheterization of the ureters in the male before The Johns Hopkins Hospital Medical Society.

Probably one of the most practical operations independently devised by Dr. Kelly was the apron method⁵ of treating complete perineal tears. I say independently, because in the *American Journal of Obstetrics*, 1899, XL, 515, Dr. Kelly says: "I find, through the kindness of Dr. Chadwick, that Dr. Warren has some time since described the apron method of treating complete tears and I desire to accord him full credit."

In 1899 Dr. Kelly digressed to write a paper on "The Recognition of the Poisonous Serpents of North America." He had long been interested in snakes and for several years many of his visitors had entered his library on Eutaw Place very cautiously, not knowing just what surprise might be in store for them. No one who was at that memorable meeting of The Johns Hopkins Hospital Medical Society the night he spoke on snakes will ever forget the tenseness of the audience; some of the brave ones sat up near the front apparently unconcerned, while the more timid migrated to the back seats, some actually sitting on the backs of the seats. When Dr. Kelly grasped a large diamond-headed rattler by the nape of the neck with his left hand, held the tail in his right hand and with the index finger of his right hand pointed out the more important marks on the snake's head, a shudder ran through the audience. A sigh of relief was clearly audible when the snake had been put back into the bag. At this moment, however, through the bag it bit Dr. Kelly's finger and the audience awaited breathlessly and in alarm for the after effects. Dr. Kelly sucked his finger, looked very pale, but went right along with his talk. In a few minutes the meeting closed and he returned home none the worse for his experience. A few hours before the meeting the snake had been teased and had discharged nearly all, if not all, of its venom.

²For a detailed description of this method see: "Hysterectomy and Hystero-Salpingo-Oophorectomy by Continuous Incision from Left to Right or from Right to Left" J. H. H. BULLETIN, 1896.

³This method was described in the *Journal of the American Medical Association*, 1898, XXXI, 1469.

⁴A more detailed report of this method appeared in the *American Journal of Obstetrics* for 1894.

⁵"A New Method of Examination and Treatment of Diseases of the Rectum and Sigmoid Flexure." *Annals of Surgery*, 1895.

In 1899 Dr. Kelly published a timely paper entitled "The Exploration of the Abdomen as an Adjunct to Every Celiotomy." We now know that when the abdomen is opened it should be most carefully explored to see that no pathological lesion has been overlooked. In 1899 few realized how essential was a systematic examination of the abdominal cavity.

In 1900 he published another epoch-making paper entitled "Ureteral Calculus; its Diagnosis by Means of the Wax-Tipped Bougie, Escape of the Calculus *per vias naturales* After Forcible Dilatation of the Ureteral Orifice." Here was a method that gave positive evidence in the majority of cases when a stone was present in the ureter and usually when one existed in the pelvis or in the kidney. At the present day the X-ray will generally reveal stones in the kidney, in the pelvis and in the ureter, but every now and then the wax-tip will show a tell-tale scratch-mark when the X-ray has failed to give any evidence of the existing calculus. The Kelly scratch-mark method is a most valuable detector of stone; it is here to stay.

In the past nearly all pelvic surgeons have encountered dense pelvic inflammatory masses so glued to one another and to the pelvic wall that their removal has been fraught with the greatest difficulty. In 1900, under the title "The Removal of Pelvic Inflammatory Masses by the Abdomen after Bisection of the Uterus," Dr. Kelly gave us a method that enables us to handle otherwise inoperable cases.⁷

In 1910 Dr. Kelly contributed to *Surgery, Gynecology and Obstetrics* a paper entitled "Lipectomy, an Operation for Removal of Redundant Fat from the Abdominal Wall." In this operation a large wedge of the redundant fat is removed and the edges of the wound in the fat and skin are then approximated. While this simple operation has given many a patient physical relief, it has a more important sphere of usefulness. Take, for example, a patient with a superabundance of fat in the lower abdomen who may have at the same time a carcinoma of the body of the uterus. In order to expose the uterus satisfactorily a very long abdominal incision must be made and the distance from the surface to the pelvis is very great. By a preliminary lipectomy the thick abdomen is converted into a very thin one at the site of the operation and the uterus can then be removed with comparative ease.

For years Dr. Kelly has been interested in the surgical treatment of cancer and was often troubled by the large number of inoperable cases presenting themselves in the clinic. He became impressed by the work of Wickham, who was a personal friend, and within a short time began the use of radium. He presented a paper on radium at a meeting of the Baltimore Medical Society, April 11, 1913, which was published in the *Maryland Medical Journal* in June, 1913, under the title "A Talk on Radium." In *International Clinics* in 1914 we find another interesting article by Dr. Kelly entitled "What Radium can Do," and in the *Journal of the American Medical Association* of the same year, "Radium in the Treatment of

Uterine Hemorrhage and Fibroid Tumors," by Dr. Kelly and Dr. Curtis F. Burnam. In the *Journal of the American Medical Association* in 1915 Kelly and Burnam gave their results with "Radium in the Treatment of Carcinomas of the Cervix Uteri and Vagina." In 1918, Professor Kelly contributed to *Surgery, Gynecology and Obstetrics* a paper entitled "Two Hundred and Ten Fibroid Tumors Treated by Radium."

From boyhood, Dr. Kelly has been greatly interested in natural history and in outdoor life and has been particularly fond of mineralogy. He spent several summers in Mexico looking carefully into the subject of mining and the extraction of precious metals. The knowledge thus obtained proved most valuable when it was definitely determined that there were deposits of radium in Colorado. Secretary Lane, of the Department of the Interior, was quick to see what an ample supply of radium would mean to the people of this country in the treatment of cancer. Dr. Kelly and Dr. James P. Douglas, of New York, undertook to extract radium from the Colorado deposits and Secretary Lane, with wise foresight, placed at their disposal the best brains of the mining experts in his department. Professor Joseph A. Holmes, head of the Bureau of Mines, rendered invaluable service in all phases of the project.

Dr. Douglas gave his share of the radium thus obtained to the General Memorial Hospital of New York, and Dr. Kelly's share came to Baltimore. Kelly and his associate, Burnam, have five grams, the largest single supply of radium in the world. The Johns Hopkins Hospital is under many obligations to them for their liberality in giving free radium treatment to many poor but worthy people who have needed such procedures at the hospital in recent years.

Let us now turn to the books published by Dr. Kelly. In 1898 there appeared from the Appleton press "Operative Gynecology," in two large volumes, which covered the subject in such a manner that it instantly commanded the attention of the surgical world both here and abroad. It was no stereotyped production; every page breathed the individuality of the author and portrayed his methods and his ideas. It also embodied the many new and improved operations that he had devised.

Shortly after Kelly decided to publish "Operative Gynecology" he asked the late Professor Franklin P. Mall where he could procure a good artist and received the name of Max Brödel, who had made excellent illustrations for Professor Karl Ludwig, the famous physiologist of Leipsic. In 1894 he secured his services. Brödel took hold with enthusiasm and with unusual fidelity pictured Kelly's operative procedures and also the gross and microscopic specimens. Not only that, he brought into the pictures such a marked degree of artistic finish that the illustrations elicited unstinted praise. By this book the professor of gynecology, already well-known, became the recognized leader in his specialty, and Brödel's illustrations set a new standard for medical illustrations in the United States. "Operative Gynecology" had numerous printings and a new edition appeared in 1906.

⁷ After publication of the approved method, Dr. Kelly found that his procedure had been anticipated by Dr. J. L. Faure, of Paris. His method, however, was devised without any knowledge of Dr. Faure's work.



DR. HOWARD A. KELLY

Dr. Kelly at 31, when he entered upon his duties as Professor of Gynecology and Obstetrics in The Johns Hopkins University, and as Gynecologist and Obstetrician in Chief to The Johns Hopkins Hospital.

In 1905 there appeared a large volume entitled "The Vermiform Appendix." The authors were Dr. Kelly and Dr. Elizabeth Hurdon. This work is a mine of information and the subject has been considered from every standpoint. It goes thoroughly into the pathology and describes the operative technique in a lucid manner. Chapters on embryology and anatomy are furnished in large part by Max Brödel, and there is an excellent bibliography. Altogether it is the best work that has ever appeared on the subject; in fact it is nearly the last word on the appendix.

In 1906 Dr. Kelly's volume on "Walter Reed and Yellow Fever" was published. Those who were at The Johns Hopkins Hospital in the early days really felt that Reed belonged to the Hopkins group. It was there that he worked with William H. Welch; it was there that we learned to love Reed, for his unassuming manner, his sterling worth and his delightful companionship. It seems but yesterday that we saw him at Union Station in Baltimore when he had come down from his summer home at Blue Ridge on his way to New York, there to catch the boat for Havana to study yellow fever. In one interested in the study of yellow fever, in the vicissitudes in the building of the Panama Canal, and in the life of the charming and brilliant scientist, this book will touch a sympathetic chord. To those of us who knew Reed it has been an inspiration.

"Gynecology and Abdominal Surgery," by Howard A. Kelly and Charles P. Noble, was published by Saunders. The first volume appeared in 1907, the second in 1908. The editors wrote extensively on the subjects in which they were particularly interested and for the remaining chapters were fortunate in securing surgeons peculiarly well adapted to treat of their special subjects. The chapters on gynecological pathology are especially valuable, being written by Dr. Elizabeth Hurdon of the gynecological department of The Johns Hopkins Hospital. "Kelly-Noble" has had an extensive and well-merited recognition by the profession.

Dr. Kelly's "Medical Gynecology" appeared in 1908. It was a work of nearly seven hundred pages and was in reality the counterpart of "Operative Gynecology"; but it appealed more especially to the general practitioner. It contained much that was of necessity omitted in "Operative Gynecology"; it has had a wide distribution, numerous printings being required and a second edition in 1912.

In 1909 Kelly and Cullen published "Myomata of the Uterus," a volume of over seven hundred pages devoted to an analysis of nearly seventeen hundred cases of uterine myomata occurring in The Johns Hopkins Hospital and in other hospitals with which the authors were connected. The development of myomata, their various degenerations, the condition of the uterine mucosa and of the adnexa were thoroughly considered, and the various operative procedures necessary were given in detail. The excellent drawings reproduced in this volume were made by Hermann Becker and August Horn.

Kelly has always been interested in his fellow-men and particularly in those who have had a large share in bringing American medicine to the forefront. In his operating room he

has had the rare privilege of coming in contact with physicians and surgeons from all parts of the country. In the social hours following the day's labor the conversation frequently drifted to a consideration of the lives of the outstanding men both past and present who had lived in the neighborhood of his guests. As a result he decided to gather in book-form short biographies of the eminent medical men and enlisted the hearty co-operation of prominent persons in all parts of the country who helped him to obtain the names of deceased physicians and surgeons and often furnished sketches of their lives.

The "Cyclopedia of American Medical Biography," comprising the lives of about eleven hundred eminent deceased physicians and surgeons from 1610-1910, published in 1912, contains a wealth of material which will become more and more appreciated as the years pass. In a biography where many judges pass upon the names of those who should be included, some omissions are inevitable. Kelly has for several years been laboring industriously over a new edition. He has been most appreciative of the constructive criticism that has been accorded the first edition, as it has already enabled him to add a number of biographies omitted in the work when first published. The American profession is under many obligations to Dr. Kelly for gathering together in book-form the life histories of the medical men of the past, men of whom this country is so justly proud.

Kelly's "History of Gynecology," found in his "Cyclopedia of American Medical Biography," is a notable piece of work. Dr. Garrison says of it: "The best account of American gynecology is the essay by Howard A. Kelly in the introduction to his 'Cyclopedia of American Medical Biography.'"

One hardly expects to find a surgeon writing on botany or botanists, but those who have been privileged to spend one or more summers with Dr. Kelly in the backwoods of Canada and have watched his enthusiasm in the study of plant and animal life were not surprised to see his attractive little book "Some American Medical Botanists in Our Botanical Nomenclature," published in 1914.

Long before Kelly came to Baltimore and while he was still laboring in Kensington he was deeply interested in the study of the bladder, ureter and kidney and from the preceding pages we have learned what a large share he has had in the development of bladder, ureteral and kidney surgery. As the years went on his interest in this field grew more intense and the results of his experience are to be found in "Diseases of the Kidneys, Ureters and Bladder, with Special Reference to the Diseases in Women," brought out by Dr. Kelly and Dr. Curtis F. Burnam in 1914.

In the early days of the hospital Dr. Kelly became acquainted with Anthony S. Murray, an enthusiastic amateur photographer, who came to the hospital each operating day to photograph the various steps of the operation and frequently the pathological specimens. Mr. Murray was beloved by every one who came in contact with him and at once became an im-

*Garrison, History of Medicine, 2. ed., Phila., W. B. Saunders. 1917. p. 861.

portant member of the happy gynecological family. Many of his photographs were used in Dr. Kelly's early papers and in articles published by other members of the staff. Mr. Murray also made many excellent lantern slides which were used in our teaching courses and at the various medical meetings.

Dr. Kelly, largely as a result of Murray's enthusiasm and excellent work, became much impressed with the value of photography as an adjunct in teaching surgery and had stereopictures made, so that students could follow clearly the steps of the various operations. Finally, he decided that it would be an admirable idea to have the operations of individual operators photographed in this manner, and thus started the "Stereo-Clinics." The work of operators in various parts of the country has been brought out in stereo-form so that to date there have been 42 sections issued. These have been published by the Southworth Company under Dr. Kelly's direction and have enabled many a surgeon in the quiet of his study to obtain a clear view of each step in a given operation. The idea proved most practical and the results have been beyond Dr. Kelly's sanguine expectations. In his enthusiastic prosecution of this work he visited many parts of this country and also England and Scotland in search of interesting and instructive subjects.

One can never forget the delightful evenings of The Johns Hopkins Hospital Historical Society. In the early days meetings were held in the library of the hospital and later when the attendance increased, in a large room under Ward H. It was a rare privilege to listen to Osler, Welch, Kelly, and others who brought with them treasured volumes. After these had been described and passed around, the speaker usually gave a short account of the author, of the school with which he had been associated and frequently of his confrères. Dr. Kelly thus presented many books and read numerous papers before the Historical Society.

Among the biographical sketches which he has published are: "Horatio Reese Holmes," 1897; "Jules Lemaire, the First to Recognize the True Nature of Wound Infection and Inflammation, and the First to Use Carbolic Acid in Medicine and Surgery," 1901; "James Carroll," 1908; "Frère Jacques," 1908; "Theodore Caldwell Janeway," 1918; "Joseph Price," 1918; and "A Tribute to Dr. W. W. Keen," 1918. Kelly's paper on John R. Young attracted unusual attention, as few had any appreciation of the fundamental work that this Marylander had accomplished. Recently Dr. Kelly gave an interesting paper on Florence Nightingale and presented to The Johns Hopkins Training School for Nurses a richly bound volume containing seven of her unpublished letters.

Dr. Kelly has been accorded distinguished recognition both in this country and abroad. He is an honorary fellow of the Chicago Gynecological Association; he was President of the Southern Surgical and Gynecological Association, one of the most active surgical societies in the United States, in 1907; President of the American Gynecological Society in 1912; Fellow of the British Gynecological Society; Honorary Fellow of the Obstetrical Society of London, of the Glasgow Obstetrical and Gynecological Society, of the Royal College of Surgeons,

Edinburgh, and of the Royal Academy of Medicine in Ireland. He is a member of the Association Française d'Urologie, Paris; of the Société d'Obstétrique, de Gynécologie et de Pédiatrie de Paris, and of the Gesellschaft der Aerzte in Wien. He is honorary member of the Società Italiana di Ostetricia e Ginecologia, Roma; of the Gesellschaft für Geburtshilfe zu Leipzig, and other societies. He was honored with an LL. D. by the University of Aberdeen in 1906, by the Washington and Lee University in 1906 and by his alma mater, the University of Pennsylvania, in 1907.

Dr. Kelly's generosity has been strikingly shown in his gifts to The Johns Hopkins Hospital. In 1905 he learned that the extensive collection of portraits collected by the late Dr. G. F. Fisher, of Sing Sing, was offered for sale. Fisher, a medical historian, an eminent practitioner and collector of books, had also accumulated valuable engravings and portraits of the leaders in medicine both in this country and in the old world. His medical library was secured for Vassar Hospital and Dr. Kelly obtained the large collection of portraits and engravings and presented them to The Johns Hopkins Hospital.

In 1897 Dr. Kelly gave to The Johns Hopkins Hospital the sum of \$5000 for a much needed addition to the gynecological operating room.

In 1901, in order to furnish additional accommodations for patients recovering from gynecological operations and to secure facilities for an examining room and laboratory in connection with the gynecological ward, Dr. Kelly, gave to the hospital the sum of \$10,000. For two years Dr. Kelly also paid the salary of a visiting nurse for the care of patients discharged from the hospital.

Probably the most valuable gift made by Dr. Kelly to The Johns Hopkins Hospital was that of a choice collection of books from his library. An extended reference to this gift appeared in THE JOHNS HOPKINS HOSPITAL BULLETIN, 1915, page 415, and is as follows: "During the past year, through the unparalleled liberality of Professor Kelly upward of four thousand volumes of books, periodicals, monographs and theses from his private library have been presented to The Johns Hopkins Hospital and placed on the shelves of the library. Many of them, and, in fact, the majority, are books connected with his own special work in gynecology and obstetrics, and represent his zeal as a collector while pursuing his special studies. They include the best treatises upon these important branches of study in German, French and English, and are invaluable for the student of medicine and the physician. They comprise many very rare works also in anatomy, medicine and general surgery, and bear remarkable testimony to the breadth of the donor's interest in the whole science of medicine."

A word of a personal nature is appropriate in such a tribute as this. Kelly, in his relations with the members of his hospital staff, has always been most kind and considerate. He

* There are many editions of Avicenna, Boerhaave, Celsus, Falloppio, Galen, Hippocrates, Vesalius; and works of Argelata, Aristoteles, Fraacastorius, Haller, Harvey, Malpighi, Rhazes, Spigelius, Sylvius, and others.

has placed responsibilities upon them and has treated them as friends and younger brothers rather than as assistants. He has given them material aid in prosecuting studies in this country or abroad and has often assisted them in bearing the expense of the publication of books and their illustrations. Many of his assistants have spent one or two years as internes, a year each as second assistant, and first assistant, and finally a year or more as resident. Under these circumstances it is not strange that many excellent men have been developed by him, who are now occupying prominent places in Baltimore and in other parts of the country. Among these may be mentioned: Hunter Robb, late of Cleveland; A. L. Stavelly, in Washington; W. W. Russell, in Baltimore; John G. Clark, in Philadelphia; Thomas S. Cullen, in Baltimore; Otto G. Ramsay, at Yale (until his untimely death); Ernest J. Stokes, in North Carolina; G. Brown Miller, in Washington; G. L. Hunner, in Baltimore; B. J. Schenck, in Detroit; John A. Sampson, in Albany; Curtis F. Burnam, in Baltimore; Henry T. Hutchins and Stephen Rushmore, in Boston; E. H. Rich-

ardson, in Baltimore; E. K. Cullen, in Detroit; Elizabeth Hurdon, in Baltimore, and many others.

The activities of Dr. Kelly have not been confined to his profession. He has been much interested in many problems of a religious and philanthropic character which have occupied no small share of his time and thoughts. He has also been a liberal contributor to many worthy philanthropic and religious enterprises.

He has taken, as a rule, a vacation of at least two months every year and for many years has occupied a delightful and simple camp in Canada. Here he has wandered through the woods, studied wild flowers and mushrooms, has taken long canoe trips and has maintained his record as a long-distance swimmer. In this way he has recruited and conserved his wonderful physical energy.

In his retirement from the active management of the Gynecological Department of The Johns Hopkins Hospital, he carries with him the cordial good wishes of his colleagues, associates, pupils and friends.

BIBLIOGRAPHY OF HOWARD A. KELLY, M. D., LL. D., HON. F. R. C. S.

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LIBRARIAN, THE JOHNS HOPKINS HOSPITAL

Dr. Kelly's bibliography covers the period from 1882 to 1919 inclusive. The 485 titles include books, pamphlets and journal articles. Most of these are in the Library of The Johns Hopkins Hospital and are of special value as gifts from Dr. Kelly.

1882

Was the thoracic duct injured in the case of President Garfield? (Correspondence). Med. News, Phila., 1882, xl, 39.

Some rare and new anomalies in man; with three cases of double femoral artery. Am. J. M. Sc., Phila., 1882, n. s., lxxxiii, 138-142.

1883

Uterus septus bicornis. Med. News, Phila., 1883, xlii, 444.

On a method of post-mortem examination of the thoracic and abdominal viscera. Through vagina, perineum, and rectum, and without incision of the abdominal parietes. Med. News, Phila., 1883, xlii, 733-734.

An improved attachment for the head-mirror. Med. News, Phila., 1883, xliii, 390.

On the mapping out of visceral diseases, in an aniline color, on the surface of the body. (Correspondence). Med. News, Phila., 1883, xliii, 417-418.

The use of oleate of aconitia as a local anodyne. Med. News, Phila., 1883, xliii, 792-793.

1884

The occurrence of the *Ascaris mystax* (Rudolphi) in the human body; with a case. Am. J. M. Sc., Phila., 1884, n. s., lxxxviii, 483-486.

The external use of the oleate of aconitia. (Correspondence). Med. News, Phila., 1884, xlv, 201-202.

Death from a pessary. Med. News, Phila., 1884, xlv, 430.

On the anæsthetic use of the hydrochlorate of cocaine upon parts of the body other than the eye. Med. News, Phila., 1884, xlv, 713-714.

1885

An ovarian cyst weighing one hundred and sixteen pounds successfully removed. Am. J. Obst., N. Y., 1885, xviii, 795-798.

Cocaine in diphtheria. Med. News, Phila., 1885, xlv, 455.

1886

A case of removal of two sessile cervical fibroid tumors by abdominal section. Am. J. Obst., N. Y., 1886, xix, 44-49.

Hydro-salpinx with congenital deficiency of tubes and broad ligaments. Am. J. Obst., N. Y., 1886, xix, 618.
Also: Med. & Surg. Reporter, Phila., 1886, liv, 712.

Cellulitic contraction of right broad ligament with disappearance of the meso-salpinx, and coherence of ovary and tube. J. Am. M. Ass., Chicago, 1886, vi, 677.

Hysterorrhaphy, or the suspension by suture of a viciously posed uterus. J. Am. M. Ass., Chicago, 1886, vii, 666.
Also: Med. News, Phila., 1886, xlix, 636.

Hæmatoma of the ovary, with adherent Fallopian tube. N. York M. J., 1886, xliii, 222.
Also: Am. J. Obst., N. Y., 1886, xix, 503-504.

Extra-uterine pregnancy; complete removal of the sac and contents; recovery. N. York M. J., 1886, xliii, 617-619.
Also: J. Am. M. Ass., Chicago, 1886, vi, 668-670.
Also: Med. & Surg. Reporter, Phila., 1886, liv, 803-806.

Ovarian tumor that weighed at normal 100 pounds. Maryland M. J., Balt., 1886, xv, 49.

Ovaries and tubes from a case of chronic ovariitis; salpingitis and pelvic peritonitis; also the right ovary and tube from a case of cellulitic contraction of right broad ligament with disappearance of the mesosalpinx and coherence of ovary and tube. Maryland M. J., Balt., 1886, xv, 49-51.
Also: Am. J. Obst., N. Y., 1886, xix, 838-841.

A unique case of extra-uterine pregnancy; complete removal of the sac and contents; recovery. With a critical examination of the cases of faradic feticide and remarks upon its dangers by R. P. Harris. Maryland M. J., Balt., 1886, xv, 51-54.
Also: Am. J. Obst., N. Y., 1886, xix, 841-843.

Asepsis not antiseptis; a plea for principles, not paraphernalia, in laparotomy. Maryland M. J., Balt., 1886, xv, 110-112.
Also: N. York M. J., 1886, xliii, 672-674.
Also: Am. J. Obst., N. Y., 1886, xix, 1076-1079.

The Munich meeting of the German Gynecological Congress. (Correspondence). Med. News, Phila., 1886, xlix, 81-82.

Gonorrhœal tubo-ovarian abscess; right side; laparotomy; removal of Fallopian tube and ovary; recovery. *Med. News, Phila., 1886, xlix, 205-207.*

Also: Am. J. Obst., N. Y., 1886, xix, 1169.

The obstetrical section of the British Medical Association. (Correspondence). *Med. News, Phila., 1886, xlix, 276-278.*

Gynæcological operations in Germany. *Med. News, Phila., 1886, xlix, 301-304.*

Hæmatoma of the ovary, with adherent Fallopian tube. *N. York M. J., 1886, xliii, 222.*

1887

Hysterorrhaphy. *Am. J. Obst., N. Y., 1887, xx, 33-46.*

Perineal and ovariectomy cushions. *Am. J. Obst., N. Y., 1887, xx, 1029-1031.*

Results of some general work in abdominal surgery, performed during seven and one-half months of 1886. *Proc. Phila. Co. M. Soc., 1887, Phila., 1888, viii, 43-50.*

Also: Polyclin., Phila., 1887, iv.

Pelvic measurements. *Obst. Gaz., Cincin., 1887, x, 123.*

Measuring the conjugata vera. *Med. News, Phila., 1887, 1, 277-278.*

A contribution to hepato-phlebotomy. *Med. News, Phila., 1887, 1, 617-619.*

Removal of the uterus through the vagina. *Med. News, Phila., 1887, ii, 276-277.*

De l'hystérorrhaphie (nouvelle opération pour le redressement de l'utérus rétrofléchi). [Abstr. transl. by E. Thomas, from: *Am. J. Obst., N. Y. J. Gaz. de gynéc., Par., 1887, ii, 65-70.*

Results of some general work in abdominal surgery, with cases and specimens. *Med. & Surg. Reporter, Phila., 1887, lvi, 425-429.*

A new leg-holder, securing a perfect lithotomy posture without assistants. *Med. & Surg. Reporter, Phila., 1887, lvi, 747.*

Letter from Leipzig. *Med. & Surg. Reporter, Phila., 1887, lvii, 210-211.*

Also: Pittsburgh M. Rev., 1887, ii.

Letter from Bremen. ["Gynecologist" tour through Germany in 1887.] *Pittsburgh M. Rev., 1887, ii.*

1888

Injuries and lacerations of the perineum and pelvic floor.

In: Syst. Pract. Gynec. (Mann), Phila., 1888, ii, 719-778.

Remarks on Alexander's operation. *Ann. Gynec., Bost., 1887-8, i, 142.*

Hysterorrhaphy. *Am. J. M. Sc., Phila., 1888, n. s., xcv, 468-481.*

Removal of the uterine appendages for disease in which pain is a prominent symptom. *Med. News, Phila., 1888, liii, 36-39.*

Also: Proc. Phila. Co. M. Soc. 1887, Phila., 1888, viii, 278-289.

Also: Maryland M. J., Balt., 1887-88, xviii, 226-231.

A case of Cæsarean section. *Med. News, Phila., 1888, liii, 320-322.*

Also: Am. J. Obst., N. Y., 1888, xxi, 1193.

Also: Polyclinic, Phila., 1888-89, vi, 117.

An aseptic two-way uterine catheter. *Med. News, Phila., 1888, liii, 326-327.*

Also: Am. J. Obst., N. Y., 1888, xxi, 721.

The Whitechapel murders. (Correspondence). *Med. News, Phila., 1888, liii, 430-431.*

Resuscitation of the asphyxiated new-born child. *Am. J. Obst., N. Y., 1888, xxi, 419-420; 421.*

A cotton packer. *Ibid., 721.*

Knife-blade tenaculum. *Ibid., 942-944.*

A self-retaining speculum. *Ibid., 945.*

Operation upon a laceration of the cervix and perineum; peritonitis; abdominal section; death. *Med. & Surg. Reporter, Phila., 1888, lviii, 489-491.*

Rubber cushions for surgical purposes. *N. York M. J., 1888, xlvii, 104-105.*

Also: Med. & Surg. Reporter, Phila., 1888, lviii, 145.

Notes explanatory of sixty-six consecutive abdominal sections recorded herewith. *Pittsburgh, M. Rev., 1888, ii, 25; 35.*

Palpation of the ureters in the female. *Tr. Am. Gynec. Soc., Phila., 1888, xlii, 50-65.*

Also: Am. J. Obst., N. Y., 1888, xxi, 1032-1034.

Discussion on the new Cæsarean section. *Tr. Am. Gynec. Soc., 1888, xlii, 130-141.*

[Remarks on Blaikie's directions for exercise.] *N. York M. J., 1888, xlvii, 136.*

Description of a new pad for general surgical purposes. *N. York M. J., 1888, xlvii, 473.*

1889

Report of twenty-five abdominal sections performed for the most part in the Kensington Hospital for Women, since the summer of 1888. *Univ. M. Mag., Phila., 1888-9, i, 400-407.*

Cholecystorrhaphy, followed by cholecystotomy; evacuation of one hundred and eighty-eight gall-stones; recovery. *Ann. Gynec., Bost., 1888-89, ii, 517-519.*

Also: Am. J. Obst., 1889, xxii, 1191-1193.

A new method of performing hysteromyomectomy. *Am. J. Obst., N. Y., 1889, xxi, 375-385.*

Hysteromyomectomy. *Boston M. & S. J., 1889, cxx, 40-41.*

Carcinoma of the corpus uteri. *Obst. Gaz., Cincin., 1889, xii, 57.*

Glass catheters. *Am. J. Obst., N. Y., 1889, xxii, 184-185.*

Kelly, H. A. & Robb, H. Craniotomy for hydrocephalus, with the use of the obstetric pad. *Univ. M. Mag., Phila., 1888-89, i, 514-519.*

1890

Diseases of the ovaries and tubes.

In: Cycl. Dis. Child., M. & S. (Keating), Phila., 1890, iii, 731-740.

On hysterorrhaphy. *Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 17-19.*

Ligation of varicose ovarian veins. *Ibid., 23.*

The more remote results of removing the ovaries and tubes. *Ibid., 57-58.*

Hysteromyomectomy. *Ibid., 96.*

Tubercular peritonitis [operation.] *Ibid., 96-97.*

A consideration of three successful Cæsarean sections in Philadelphia. *Am. J. Obst., N. Y., 1890, xxiii, 225-246.*

Supra-vaginal hysterectomy. Hysteromyomectomy with suspension of the stump in the lower angle of the abdominal incision. *Med. News, Phila., 1890, lvi, 695-698.*

Treatment of recto-vaginal fistulae. (Editorial). *Med. News, Phila., 1890, lvii, 516-517.*

Cephalhæmatoma. A case of sub-pericranial blood-tumor in the new-born child. *Med. News, Phila., 1890, lvii, 229-231.*

A successful Cæsarean section for a large bony tumor choking the pelvis. *Med. & Surg. Reporter, Phila., 1890, lxii, 100-106.*

The gynecological operating room in The Johns Hopkins Hospital, and the antiseptic and aseptic rules in force. *Johns Hopkins Hosp. Rep., Balt., 1890, ii, 131-139.*

The report of the autopsies in two cases dying in the Gynecological wards without operation. *Johns Hopkins Hosp. Rep., Balt., 1890, ii, 167-176.*

Composite temperature and pulse charts of forty cases of abdominal section. *Johns Hopkins Hosp. Rep., Balt., 1890, ii, 177-183.*

The gonococcus in pyosalpinx. *Johns Hopkins Hosp. Rep., Balt., 1890, ii, 195-200.*

Tuberculosis of the Fallopian tubes and peritoneum; ovarian tumor; removal of the ovaries and Fallopian tubes with drainage, followed by recovery; demonstration of the tubercle bacillus in sections of the tube. *Johns Hopkins Hosp. Rep., Balt., 1890, ii, 201-204.*

General gynecological operations from October 15, 1889, to March 4, 1890. *Johns Hopkins Hosp. Rep., Balt., 1890, ii, 205-215.*

Ligature of the trunks of the uterine and ovarian arteries as a means of checking hemorrhage from the uterus and broad ligaments in abdominal operations. *Johns Hopkins Hosp. Rep., Balt., 1890, ii, 220-223.*

Elephantiasis of the clitoris. Johns Hopkins Hosp. Rep., Balt., 1890, ii, 227-230.

Kolpo-ureterotomy; incision of the ureter through the vagina, for the treatment of ureteral stricture. Johns Hopkins Hosp. Rep., Balt., 1890, ii, 234-242.

Record of deaths following gynecological operations. Abstracted from the records of the pathological department. Johns Hopkins Hosp. Rep., Balt., 1890, ii, 243-252.

Extra-uterine pregnancy. Review and discussion. Paper read before the Obstetrical and Gynecological Society of Baltimore City, January 14 and February 11, 1890. Tr. Obst. & Gynec. Soc., Balt., 1890, 33-48.

Vaginal puncture and drainage for pelvic abscess. An address before the Gynecological and Obstetrical Society of Washington, December 5, 1890. (Not published).

Cephalematoma verum externum; sub-pericranial blood-tumor of the new-born. Tr. Am. Gynec. Soc., Phila., 1890, xv, 189-209.

Kelly, H. A. & Chriskey, A. A. Report of the urinary examination of ninety-one gynecological cases. Johns Hopkins Hosp. Rep., Balt., 1890, ii, 216-219.

Kelly, H. A. & Robb, H. The laparotomies performed in the gynecological department from October 16, 1889, to March 3, 1890. Johns Hopkins Hosp. Rep., Balt., 1890, ii, 141-166.

1891

A death caused by a uterine dilator, with some remarks as to the proper method of using the dilator. Am. J. Obst., N. Y., 1891, xxiv, 42-46.

The palpation of normal ovaries. Am. J. Obst., N. Y., 1891, xxiv, 129-142.

The steps of the Cæsarean section; the do's and the don't's. Am. J. Obst., N. Y., 1891, xxiv, 532-544.

Hand disinfection. Am. J. Obst., N. Y., 1891, xxiv, 1414-1419.

The ideal dressing for the abdominal wound. Am. J. Obst., N. Y., 1891, xxiv, 1439-1441.

Abstracts from "The picture of Philadelphia," etc. Read before the Historical Society of the Johns Hopkins Hospital. Med. News, Phila., 1891, lviii, 197-198.

Cancer of the cervix uteri in the negro; physometra in the negro, due to cancer; mania following operation; recovery. Tr. South. Surg. & Gynec. Ass., 1890, Phila., 1891, iii, 386-390.

Antisepsis and asepsis before and after major gynecological operations. Am. J. M. Sc., Phila., 1891, n. s., cl, 44-55.

Letter to Dr. G. H. Kirwan. [The modern treatment of wounds, by G. H. Kirwan.] Lehigh Valley M. Mag., 1890-1891, ii, 213-214.

Report from Gynecological Clinic. (A case of tubercular peritonitis treated with Koch's lymph). Johns Hopkins Hosp. Bull., Balt., 1891, ii, 15.

Twin pregnancy. Breech and transverse presentation. The placenta and the membranes. (Proc. Johns Hopkins Hosp. Med. Soc., Dec. 15, 1890). *Ibid.*, 44.

The treatment of large myomatous tumors of the uterus. Myotomy and hysteromyomectomy. *Ibid.*, 45-49.

A case of conservative Cæsarean section. (Proc. Johns Hopkins Hosp. Med. Soc., Feb. 2, 1891). *Ibid.*, 62.

Israel Spachius's Gynecology. (Proc. Johns Hopkins Hosp. Hist. Club, Oct. 12, 1891). *Ibid.*, 164.

My fourth Cæsarean section. N. York M. J., 1891, lili, 500-503.

1892

Diseases of the broad ligaments, tubes, and ovaries.

In: Syst. Pract. Therap. (Hare), Phila., 1892, iii, 803-834.

The ministry of nursing. An address delivered to the second class of nurses graduating at The Johns Hopkins Hospital, June 3, 1892. Balt., 1892, Griffin, Curley & Co., 14 p. 8°.

A letter to my assistant on the method of securing asepsis in the preparation of instruments, ligatures, and dressings in my private office. Am. J. Obst., N. Y., 1892, xxv, 184-189.

The ureteral catheter. Am. J. Obst., N. Y., 1892, xxv, 768-771.

Clinical report of cystectomy for polycystic ovarian tumor. Med. & Surg. Reporter, Phila., 1892, lxxvii, 241-246.

Confinement on the obstetric pad. Med. Rec., N. Y., 1892, xlii, 663.

Gynecological technique; a brief summary of the principles involved, as well as the technique of the gynecological operations performed in The Johns Hopkins Hospital; the significance of the operation and its technical surroundings to gynecological practice. N. York J. Gynec. & Obst., 1892, ii, 667-674.

Address to nurses. Delivered at the third annual commencement of the Training School for Nurses of Wilkes Barre City Hospital, July 1, 1892.

In: Rep. 3d ann. comm. Training School for Nurses, Wilkes Barre City Hosp., 1892.

Presentation of Foesius' Hippocrates. (Proc. Johns Hopkins Hosp. Hist. Club, March 14, 1892). Johns Hopkins Hosp. Bull., Balt., 1892, iii, 43.

On methods of illustrating lectures with a lantern-slide exhibition of injuries at the vaginal outlet. Times & Reg., Phila., 1892, xxiv, 649-650.

1893

Drainage in abdominal surgery. Practice, Richmond, 1893, viii, 69-70.

My recent ureteral work. Ann. Gynec. & Pediat., Phila., 1892-93, vi, 449-460.

Catheterization of the ureters. Ann. Gynec. & Pædiat., Phila., 1892-93, vi, 641-644.

The ethical side of the operation of oöphorectomy. Am. J. Obst., N. Y., 1893, xxvii, 206-208.

Glass trocars for tapping large ovarian cysts. Am. J. Obst., N. Y., 1893, xxvii, 581.

The best needle holder. Am. J. Obst., N. Y., 1893, xxvii, 870-872.

The examination of the female bladder and the catheterization of the ureters under direct inspection. Johns Hopkins Hosp. Bull., Balt., 1893, iv, 101-102.

Extra-uterine pregnancy treated by vaginal incision. Johns Hopkins Hosp. Bull., Balt., 1893, iv, 109.

A case of uterus duplex solidus, with atresia of the vagina and cervix. Johns Hopkins Hosp. Bull., Balt., 1893, iv, 109-110.

Exhibition of a convalescent case of peritonitis due to ruptured tubal abscess. Johns Hopkins Hosp. Bull., Balt., 1893, iv, 111-112.

Suspensio uteri. J. Am. M. Ass., Chicago, 1893, xxi, 332-333.

Prolapsus uteri. N. Am. Pract., Chicago, 1893, v, 337-347.

The early treatment of carcinoma uteri. N. York M. J., 1893, lviii, 433-434.

The examination under anæsthesia: its uses and its limitations. N. York M. J., 1893, lviii, 617-618.

A preliminary report on the morphology of ovarian and myomatous tumors. N. York J. Gynec. & Obst., 1893, iii, 465-484. Also: Tr. South. Surg. & Gynec. Ass., 1892, Phila., 1893, v, 211-217. Also: Am. J. Obst., N. Y., 1893, xxvii, 310-312.

Epitome of an address on sepsis, antisepsis and asepsis, in relation to operative gynecology. Tr. M. Soc., N. Y., Phila., 1893, 375-377.

Abstract of a paper on urinalysis in gynecology. Am. Med. Surg. Bull., N. Y., 1893, vi, 934-935. Also: Am. J. Obst., N. Y., 1893, xxviii, 429-431.

1894

The technique of gynecological operations.

In: Am. Text-Bk. Gynec. (Baldy), Phila., 1894, 54-80.

Lacerations of the soft parts.

In: Am. Text-Bk. Gynec. (Baldy), Phila., 1894, 245-266.

Genital fistula.

In: Am. Text-Bk. Gynec. (Baldy), Phila., 1894, 267-277.

Diseases of the urethra, bladder, and ureters.

In: Am. Text-Bk. Gynec. (Baldy), Phila., 1894, 615-659.

The gynecological operating room. Johns Hopkins Hosp. Rep., Balt., 1892-4, iii, 301-302.

An external direct method of measuring the conjugata vera. Johns Hopkins Hosp. Rep., Balt., 1892-94, iii, 303-309.

- Prolapsus uteri without vesical diverticulum, and with anterior enterocele. *Ibid.*, 311-320.
- Lipoma of the labium majus. *Ibid.*, 321-326.
- Deviations of the rectum and sigmoid flexure associated with constipation a source of error in gynecological diagnosis. *Ibid.*, 327-342.
- Operations for the suspension of the retroflexed uterus. *Ibid.*, 343-358.
- Gynecological operations not involving celiotomy. Tabulated by A. L. Stavelly. *Ibid.*, 377-410.
- The employment of an artificial retro-position of the uterus in covering extensive denuded areas about the pelvic floor. *Ibid.*, 411-417.
- Some sources of hemorrhage in abdominal pelvic operations. *Ibid.*, 419-422.
- Traumatic atresia of the vagina with hematokolpos and hæmatometra. *Ibid.*, 429-431.
- Resuscitation in chloroform asphyxia. *Ibid.*, 507-508.
- Abdominal operations performed in the gynecological department from March 5, 1890, to December 17, 1892. *Ibid.*, 547-673.
- A study of intra-abdominal pressure with practical deductions. Cleveland M. Gaz., 1893-94, ix, 239-247.
- The diagnosis of pelvic inflammatory diseases. Ann. Gynec. & Pediat., Phila., 1893-94, vii, 185-190.
- Uretero-ureteral anastomosis; uretero-ureterostomy. [Remarks by Dr. Bloodgood.] Johns Hopkins Hosp. Bull., Balt., 1893, iv, 89-90.
Also: Ann. Surg., Phila., 1894, xix, 70-77.
- The direct examination of the female bladder with elevated pelvis; the catheterization of the ureters under direct inspection, with and without elevation of the pelvis. Am. J. Obst., N. Y., 1894, xxix, 1-19.
Also: Johns Hopkins Hosp. Bull., Balt., 1894, v, 16.
- The cystoscope. Am. J. Obst., N. Y., 1894, xxx, 85-90.
- Resuscitation, from impending death due to concealed hemorrhage, by an infusion of a litre of normal salt solution centrally into the radial artery. Am. J. Obst., N. Y., 1894, xxx, 184-189.
- Electric illumination of the field in abdominal surgery. Am. J. Obst., N. Y., 1894, xxx, 348-353.
- The advantage of atmospheric distention of the rectum, with dislodgment of the small intestines, in the bimanual examination of uterus, ovaries, and tubes. Am. J. Obst., N. Y., 1894, xxix, 607-610.
- An improved lock for paired instruments. Ann. Surg., Phila., 1894, xix, 231-235.
- Dysmenorrhœa. N. York J. Gynec. & Obst., 1894, iv, 408-411.
Also: Tr. M. Soc. N. Y., Albany, 1894, 177-181.
- Introduction of bougies into the ureters preceding hysterectomy and the removal of densely-adherent structures adjacent to the ureter. (Proc. Johns Hopkins Hosp. Med. Soc., Dec. 18, 1893.) Johns Hopkins Hosp. Bull., Balt., 1894, v, 17.
- Lantern slides as an aid to clinical teaching. (Proc. Johns Hopkins Hosp. Med. Soc., Jan. 15, 1894.) *Ibid.*, 35.
- The methods employed in securing statistical tables for Emmet's Gynecology. Exhibition of original tables presented by Dr. Emmet. (Proc. Johns Hopkins Hosp. M. Soc., Feb. 19, 1894.) *Ibid.*, 51-52.
- Ligation of both internal iliac arteries for hemorrhage in hysterectomy for carcinoma uteri. (Proc. Johns Hopkins Hosp. M. Soc., March 5, 1894.) *Ibid.*, 53-54.
- Myoma complicating pregnancy and preventing delivery. Porro-Cæsarean operation modified by dropping the pedicle. (Proc. Johns Hopkins Hosp. Med. Soc., April 2, 1894.) *Ibid.*, 80-81.
- Infusion of normal saline solution in connection with gynecological operations and the accidental hemorrhages of parturition. (Proc. Johns Hopkins Hosp. Med. Soc., April 2, 1894.) *Ibid.*, 81-82.
- Recent results in hysteromyomectomy. (Proc. Johns Hopkins Hosp. Med. Soc., May 7, 1894.) *Ibid.*, 99-100.
- Ureterotomy. *Ibid.*, 137.
- A new method of exploring the rectum and sigmoid flexure. *Ibid.*, 137-138.
- Recent results in hysteromyomectomy. The direct examination of the female bladder and catheterization of the ureters under direct inspection. [n. p., 1894, *vel subseq.*] 8°.
- Kelly, H. A., & Cullen, T. S. Record of deaths occurring in the gynecological department from June 6, 1890, to May 4, 1892. Abstracted from the autopsy notes of the pathological department. Johns Hopkins Hosp. Rep., Balt., 1892-94, iii, 675-762.
- Kelly, H. A. & Sherwood, Mary. One hundred cases of ovariectomy performed on women over seventy years of age. *Ibid.*, 509-545.
- 1895
- Extra-uterine pregnancy.
In: Am. Text-Bk. Obst. (Norris & Dickinson), Phila., 1895, 273-294.
- Diseases of the female bladder and urethra.
In: Twentieth Cent. Pract., N. Y., 1895, i, 663-726.
- Diagnosis of ureteral and renal diseases in women. J. Am. M. Ass., Chicago, 1895, xxv, 272-274.
- Suspensio uteri—the proper method of performing it, and its results. (Abstr.) J. Am. Med. Ass., Chicago, 1895, xxv, 318.
- Suspension of the uterus; the operative treatment of retroflexion based on a consideration of 200 cases. J. Am. M. Ass., Chicago, 1895, xxv, 1079-1081.
- Diagnosis of renal calculus in women. Med. News, Phila., 1895, lxvii, 593-596.
- Gonorrhœal pyelitis and pyo-ureter cured by irrigation. Johns Hopkins Hosp. Bull., Balt., 1895, vi, 19-21.
- Uretero-cystostomy performed seven weeks after vaginal hysterectomy. *Ibid.*, 27-28.
- Sigmoido-proctostomy; an anastomosis of the lumen of the sigmoid flexure through the lateral wall of the rectum at the pelvic floor, without suture. *Ibid.*, 30-31.
Also: Mathews' M. Quart. Louisville, 1895, ii, 212-216.
- A new method of examination and treatment of diseases of the rectum and sigmoid flexure. Ann. Surg., Phila., 1895, xxi, 468-478.
Also: [Abstr.] Centralb. f. Chir., Leipzig., 1895, xx, 961-962.
- "Female" or woman. (Correspondence). Am. J. Obst., N. Y., 1895, xxxi, 394.
Also: Pittsburgh M. Rev., 1895, ix, 160.
- The renal catheter and its use in the diagnosis and treatment of renal diseases. Tr. Am. Gynec. Soc., Phila., 1895, xx, 20-29.
Also: Boston M. & S. J., 1895, cxxxiii, 469.
Also: Am. J. Obst., N. Y., 1895, xxxii, 120-123.
- 1896
- State regulation of the social evil. Washington, 1896, Purity Publ. Co., 15 p. 8°.
- Personal purity. Health Mag., Wash., 1895-96, iii, 590-596.
- A criticism on Prof. Howard A. Kelly and his discoveries in the domain of urinary diseases, by W. Rubeska, M.D. My work on the diseases of the urinary tract in women. Being a reply to the above. (Correspondence). Am. J. Obst., N. Y., 1896, xxxiii, 394-405.
- Meine Arbeit über die Krankheiten der weiblichen Harnwege. Antwort auf Mittheilungen des Herrn Prof. W. Rubeska. Centralb. f. Gynäk., Leipzig, 1896, xx, 489-498.
- Five cases of ovariectomy in women over seventy years of age. Am. J. Obst., N. Y., 1896, xxxiv, 222-227.
- A reply to Prof. Pawlik's claim to the discovery of my method of examining the bladder and catheterizing the ureters in women. Am. J. Obst., N. Y., 1896, xxxiv, 259-261.
- Delivery by traction on the scalp of the child. Am. J. Obst., N. Y., 1896, xxxiv, 356-357.
- Conservatism in ovariectomy. J. Am. M. Ass., Chicago, 1896, xxvi, 249-251.
- Unchastity and credibility. (Letter to the editor of the *Journal of the American Medical Association*). J. Am. M. Ass., Chicago, 1896, xxvi, 992-993.
- The treatment of large vesico-vaginal fistulæ. Johns Hopkins Hosp. Bull., Balt., 1896, vii, 29-30.
Also: Am. J. Obst., N. Y., 1896, xxxiii, 930-931.

Nephro-ureterectomy; extirpation of the kidney and ureter simultaneously. *Johns Hopkins Hosp. Bull., Balt., 1896, vii, 31-37.*

The treatment of pyo-ureteritis and pyonephrosis by ureteral and renal catheters. *Ibid., 48-50.*

Women in medicine. *Ibid., 50-52.*

The treatment of ectopic pregnancy by vaginal puncture. (Proc. Johns Hopkins Hosp. Med. Soc., Oct. 19, 1896.) *Ibid., 209-211.*

Hysteromyomectomy and hystero-salpingo-oöphorectomy by continuous incision from left to right or from right to left. *Tr. South. Surg. & Gynec. Ass., 1895, Phila., 1896, viii, 133-138.*
Also: *Johns Hopkins Hosp. Bull., Balt., 1896, vii, 27-29.*

The treatment of extra-uterine pregnancy, ruptured in early months, by vaginal puncture and drainage. *Am. Gynec. & Obst. J., N. Y., 1896, ix, 129-151.*

Also: *Tr. Am. Gynec. Soc., Phila., 1896, xxi, 180-208.*

Also: *Am. J. Obst., N. Y., 1896, xxxiv, 103-105.*

The treatment of backward displacements of the uterus. *Am. J. M. Sc., Phila., 1896, n. s., cxii, 629-649.*

[Letter to the editor of the *Medical News* in regard to Dr. Pryor's article, entitled "A new and rapid method of dealing with intra-ligamentary fibromyomata." *Med. News, N. Y., 1896, lxviii, 501.*

Some recent important advances in the diagnosis and treatment of urinary diseases in women. *Pittsburgh M. Rev., 1896, x, 1-8.*

Abdominal hysterectomy for fibroma uteri. *South. Pract., Nashville, 1896, xviii, 7-21.*

Entgegnung an Prof. Dr. Pawlik. *Centrabl. f. Gynäk., Leipz., 1896, xx, 1266-1273.*

Use of the renal catheter in the diagnosis of stone in the kidney. *Maryland M. J., Balt., 1896, xxv, 100.*

The Johns Hopkins Medical Students. (Correspondence). *Pittsburgh M. Rev., 1896, x, 315.*

Ovarian cysts weighing over one hundred pounds. Read at the Johns Hopkins Hospital Medical Society. May 18, 1896. (Not published).

1897

The sources and diagnosis of pyuria. *Med. News, N. Y., 1897, lxxi, 756-761.*

Also: *Tr. South. Surg. & Gynec. Ass., 1897, Phila., x, 99-124.*

Also: *Am. J. Surg. & Gynec., St. Louis, 1898-99, xi, 55-56.*

Excision of a parovarian cyst without removal of its ovary or tube. *Johns Hopkins Hosp. Bull., Balt., 1897, viii, 50-51.*

Horatio Reese Holmes, 1856-96. *Tr. Am. Gynec. Soc., Phila., 1897, xxii, 310-312.*

The conservative treatment of myomatous uteri. *J. Am. M. Ass., Chicago, 1897, xxix, 668-669.*

Operative treatment of pelvic inflammatory disease. *Compt. rend. Cong. périod. internat. de gynec. et d'obst. 2. sess., 1896, Genève, 1897, 133-150.*

Address before the Central College of Physicians and Surgeons of Indianapolis on method of ureteral catheterization. *Indiana M. J., 1897, xvi, 211-214.*

Kelly, H. A. & Ramsay, O. De l'usage du cathéter rénal dans le diagnostic et le traitement des maladies des reins et des urètres. *Rev. de gynec. et de chir. abd., Par., 1897, 823-842.*

Kelly, H. A., Noble, C. P. [et al.]. Abdominal hysterectomy for fibroma uteri. *South. Pract., Nashville, 1897, xix, 7-21.*

1898

Operative gynecology. 2 v. N. Y., 1898. D. Appleton & Co. 581 p. 557 p. 24 pl. 8°.

Conservation of the ovary in hysterectomy and hystero-myomectomy. *Brit. M. J., Lond., 1898, i, 288-291.*

Ureteral anastomosis. *Am. Gynec. & Obst. J., N. Y., 1898, xii, 725-741.*

The hand basins in use in surgical operating rooms. *Am. J. Obst., N. Y., 1898, xxxvi, 188-193.*

The preservation of the hymen. *Am. J. Obst., N. Y., 1898, xxxvii, 7-14.*

The catheterization of the ureters in the male through an open cystoscope with the bladder distended with air by posture. *Johns Hopkins Hosp. Bull., Balt., 1898, ix, 62.*

A preliminary report upon the examination of the bladder and the catheterization of ureters in men. *Ann. Surg., Phila., 1898, xxvii, 71-73.*

Cystoscopy and catheterization of the ureters in the male. *Ann. Surg., Phila., 1898, xxvii, 475-486.*

Catgut sutures and ligatures. *Med. News, N. Y., 1898, lxxiii, 293-294.*

Bactériologie de l'appareil génital de la femme. *Tr. S. Bonnet, Semaine gynéc., Par., 1898, iii, 268.*

Principes généraux concernant les opérations plastiques. [Transl.] *Semaine gynéc., Par., 1898, iii, 353-356.*

The treatment of complete rupture of the perineum by dissecting out the sphincter muscle and its direct union by buried sutures. *J. Am. M. Ass., Chicago, 1898, xxxi, 1469.*

Also: *Maryland M. J., Balt., 1899, xli, 29.*

Also: *Memphis Lancet, 1899, ii, 29-32.*

Also: *Am. J. Obst., N. Y., 1899, xxxix, 216-217.*

Discussion on the papers of Drs. Smith and Pryor. *Tr. Am. Gynec. Soc., Phila., 1898, xxiii, 59-61.*

Abdominal myomectomy. *Ibid., 221-239.*

Discussion: Should non-absorbable ligatures be discarded in gynecological surgery. *Ibid., 262-265.*

Discussion on the papers of Drs. Dudley and Bovee. *Ibid., 284-286.*

Kelly, H. A., & MacCallum, W. G. Pneumaturia. *J. Am. M. Ass., Chicago, 1898, xxxi, 375-381.*

1899

The operation for complete tear of the perineum. *Am. J. Obst., N. Y., 1899, xl, 202-213.*

Also: *Tr. Am. Gynec. Soc., 1899, xxiv, 186-202.*

Some new instruments to facilitate the operation of myomectomy. *Am. J. Obst., N. Y., 1899, xl, 218-221.*

A new handle and grip for scissors for plastic and other delicate work. *Ibid., 229-233.*

The use of the renal catheter in determining the seat of obscure pain in the side. *Ibid., 328-334.*

The reflux of air into the ureters through the air-distended bladder in the knee-breast posture. *Ibid., 468-470.*

The apron method of treating complete tear of the perineum. (Correspondence). *Ibid., 515.*

A curette for cervical cancer. *Ibid., 829-830.*

The dissection and liberation of the sphincter and muscle followed by its direct suture in cases of complete tear of the perineum, with a splinting suture passing between the outer and inner margins of the muscle. *Johns Hopkins Hosp. Bull., Balt., 1899, x, 1-7.*

A new operation for vesico-vaginal fistula. (Proc. Johns Hopkins Hosp. Med. Soc., Feb. 6, 1899.) *Ibid., 115.*

New use for renal catheters. (Proc. Johns Hopkins Hosp. Med. Soc., Feb. 20, 1899.) *Ibid., 116.*

Report of gynecological cases: I. Extensive destruction of the sphincter; II. Carcinoma uteri; III. Excessive growth of fat. (Proc. Johns Hopkins Hosp. Med. Soc.) *Ibid., 196-197.*

The recognition of the poisonous serpents of North America. *Ibid., 217-221.*

Further uses of the ureteral catheter. *Maryland M. J., Balt., 1899, xli, 141.*

A new operation for vesicovaginal fistula. *Ibid., 106.*

A new method of treating complete tear of the rectovaginal septum by turning down an apron into the rectum and by buried suture through the sphincter muscle. *Med. News, N. Y., 1899, lxxv, 334-335.*

The exploration of the abdomen as an adjunct to every celiotomy. *Med. News, N. Y., 1899, lxxv, 784-788.*

Also: *Ann. Gynec. & Pediat., Bost., 1900, xlii, 322-324.*

1900

An improved vesical speculum. *Am. J. Obst., N. Y., 1900, xlii, 818-823.*

- The evolution of my technique in the treatment of fibroid uterine tumors. *Am. J. Obst., N. Y.*, 1900, xlii, 289-307.
Also: *Tr. Am. Gynec. Soc., Phila.*, 1900, xxv, 207-221.
- The removal of pelvic inflammatory masses by the abdomen after bisection of the uterus. *Am. J. Obst., N. Y.*, 1900, xlii, 818-839.
Also: Nashville *J. M. & S.*, 1900, lxxviii, 208-211.
Also: *Am. J. Surg. & Gynec., St. Louis*, 1901, xiv, 91-92.
Also: *Ann. Gynec. & Pediat., Boston*, 1901, xiv, 174-177.
Also: *Johns Hopkins Hosp. Bull., Balt.*, 1901, xii, 1-4.
- A new method of making applications to the vaginal vault, and a new instrument to facilitate cleansing the vagina in leucorrhœa. *Am. Gynec. & Obst. J., N. Y.*, 1900, xvi, 193-195.
- Notes on an improved method of removing the cancerous uterus by the vagina. *Johns Hopkins Hosp. Bull., Balt.*, 1900, xi, 55-56.
- A preliminary report on the surgical treatment of complicated fibroid tumors of the womb, with a description of two methods of operating. *Ibid.*, 56-58.
- Poisonous snakes. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Feb. 5, 1900.) *Johns Hopkins Hosp. Bull., Balt.*, 1900, xi, 73.
- Uncontaminated urine. *Ibid.*, 91-92.
- A note on a series of new vesical specula. *Ibid.*, 93.
- Ureteral calculus; its diagnosis by means of the wax-tipped bougie. Escape of the calculus *per vias naturales* after forcible dilatation of the ureteral orifice. *J. Am. M. Ass., Chicago*, 1900, xxxiv, 515-517.
- The present status of operations for cancerous uteri. *Ibid.*, 1215-1220.
- Resection and anastomosis of the divided ureter. *J. Am. M. Ass., Chicago*, 1900, xxxv, 860-863.
- A rapid and simple operation for gall-stones found by exploring the abdomen in the course of a lower abdominal operation. *Med. News, N. Y.*, 1900, lxxvii, 959-963.
- What precautions shall we take to avoid leaving foreign bodies in the abdomen after operations? *N. York M. J.*, 1900, lxxi, 405-407.
- Normal prophylactic appendectomy. *Med. Rev., St. Louis*, 1900, xli, 207.
- Medical Sermonets. No. 21. A plea for the humanities in nursing. *Phila. M. J.*, 1900, vi, 179-180.
- Methods of teaching gynecology. *Phila. M. J.*, 1900, vi, 391-393.
Also: *Indian M. Rec., Calcutta*, 1901, xx, 105-107.
- Gynecology, its present, past and future. *Phila. M. J.*, 1900, vi, 550-551.
- Kelly, H. A., & Brown, T. R. A note on the use of nitrous oxid and ether as an anæsthetic. *Phila. M. J.*, 1900, vi, 869-871.
- 1901
- Diseases of the ovaries and Fallopian tubes.
In: *Cycl. Dis. Child., M. & S. (Keating)*, *Phila.*, 1901, v, 906-930.
- Necessity of employing the newer methods of diagnosis in rectal and urinary diseases. *Tr. Am. Surg. Ass., Phila.*, 1901, xix, 216-218.
- Kircher et Lemaire 1658-1900. *Rev. de gynec. et de chir. abd.*, *Par.*, 1901, v, 829-850.
- Erythrim from external stem pessary. *Am. J. Obst., N. Y.*, 1901, xliii, 72.
- A new and better method of opening and of draining the bladder in women. *Am. J. Obst., N. Y.*, 1901, xliiv, 23-25.
- Scratch-marks on the wax-tipped catheter as a means of determining the presence of stone in the kidney and in the ureter. *Am. J. Obst., N. Y.*, 1901, xliiv, 441-454.
- How to deal with the vermiform appendix. Some forms of complicated appendicitis. *Am. Med., Phila.*, 1901, i, 109-110.
- A historical note upon diptera as carriers of diseases, *Paré, Déclat.* *Johns Hopkins Hosp. Bull., Balt.*, 1901, xii, 240-242.
- Drainage of the bladder and cystoscopic examinations. *Johns Hopkins Hosp. Bull., Balt.*, 1901, xii, 298.
- Jules Lemaire. The first to recognize the true nature of wound infection and inflammation, and the first to use carbolic acid in medicine and surgery. *J. Am. M. Ass., Chicago*, 1901, xxxvi, 1083-1088.
- Discussion of Dr. A. H. Cordier's paper "Post-operative hemorrhage." *J. Am. M. Ass., Chicago*, 1901, xxxvii, 18.
- Some further notes on the extension of the principle of bisection in abdominal surgery. *St. Paul M. J.*, 1901, iii, 380-386.
- Kelly, H. A. & Faure, J. L. L'extirpation des masses inflammatoires pelviennes par l'abdomen, après hémi-section de l'utérus. [*Trad.*] *Gynécologie, Par.*, 1901, v, 260-279.
- 1902
- Extra-uterine pregnancy.
In: *Am. Text-Bk. Obst.*, 2. ed. (Norris & Dickinson), *Phila.*, 1902, 324-346.
- Nephrectomy; panhystero-myomectomy, with double salpingo-oophorectomy and appendicectomy; fixation of right kidney; suspension of uterus, with resection of a corpus luteum hæmatoma; salpingo-oophorectomy, followed by resection of the sigmoid for carcinoma. *Internat. Clin., Phila.*, 1902, 12. s., ii, 232-246.
- Some notes upon the management of a modern private hospital. *Internat. Clin., Phila.*, 1902, 12. s., ii, 261-273.
- The mimicry of pregnancy by fibroid and ovarian tumors. *Am. Gynec., N. Y.*, 1902, i, 449-462.
- Further notes on the uses of the wax-tipped catheter in the diagnosis of stone in the kidney or ureter. *Am. J. Obst., N. Y.*, 1902, xlii, 66-70.
- On methods of incising, searching, and suturing the kidney. *Brit. M. J., Lond.*, 1902, i, 256-261.
- Exhibition of a case of pelvic tuberculosis. *Johns Hopkins Hosp. Bull., Balt.*, 1902, xliii, 141-142.
- The treatment of vesico-vaginal and recto-vaginal fistulæ high up in the vagina. *Johns Hopkins Hosp. Bull., Balt.*, 1902, xliii, 73-74.
Also: *Indian M. Rec., Calcutta*, 1902, xxii, 632-634.
- The true spirit of the nursing profession. An address at the annual meeting of the visiting nurse association of Baltimore. *Johns Hopkins Nurses Alumnae Mag.*, *Balt.*, 1901-2, i, 117-119.
- The advantages of the knee-chest posture in some operations upon the vesical end of the ureters. *J. Am. M. Ass., Chicago*, 1902, xxxix, 291-293.
- Stricture of the ureter. *J. Am. M. Ass., Chicago*, 1902, xxxix, 363-368.
- Under what circumstances is it advisable to remove the vermiform appendix when the abdomen is opened for other reasons? *J. Am. M. Ass., Chicago*, 1902, xxxix, 1019-1021.
- 1903
- Labia urethræ and Skene's glands. *Am. Med. Phila.*, 1903, vi, 429-431; 465-468.
Also: *Ann. Gynec. & Pediat., Bost.*, 1903, xvi, 104-108.
- Removal of vesical papilloma through an incision in the septum with the patient in the knee-chest posture. *Am. J. Obst., N. Y.*, 1903, xlvii, 28-31.
- Instruments for use through cylindrical rectal specula with the patient in the knee-chest posture. *Ann. Surg., Phila.*, 1903, xxxvii, 924-927.
- Les débuts de l'histoire de l'appendicite en France. *Bull. et mém. Soc. de chir. de Par.*, 1903, n. s., xxix, 632-649.
Also: *Presse méd., Par.*, 1903, i, 437-441.
- The early history of appendicitis in Great Britain. *Glasgow M. J.*, 1903, ix, 81-97.
- The selection of methods in abdominal hysterectomy. *Glasgow M. J.*, 1903, ix, 241-254.
Also: *J. Obst. & Gynec. Brit. Emp., Lond.*, 1903, iv, 343-354.
- A method of sequestering the urinary bladder in extensive operations involving its peritoneal surfaces. *Johns Hopkins Hosp. Bull., Balt.*, 1903, xiv, 96-98.
- The danger of methods often used at present in dusting waiting-rooms, cars, and other public places. *J. Am. M. Ass., Chicago*, 1903, xli, 861-862.

Indications for particular methods in extirpating the diseased pelvic viscera. *Lancet*, Lond., 1903, ii, 30-32.

The expansion of a specialty. *Med. Rec.*, N. Y., 1903, lxxii, 693-698.

1904

My experience with the renal catheter as a means of detecting renal and ureteral calculi. *Am. J. Urol.*, N. Y., 1904, i, 14-21.

Ideal method of removing the vermiform appendix. *Am. Med.*, Phila., 1904, viii, 1123-1125.

Myomectomy in its relation to pregnancy. (*Proc. Johns Hopkins Hosp. Med. Soc.*, March 7, 1904.) *Johns Hopkins Hosp. Bull.*, Balt., 1904, xv, 259.

The piezometer, an instrument for measuring resistances. *Ibid.*, 293.

Injuries to the rectum caused by gynecologic examinations. *J. Am. M. Ass.*, Chicago, 1904, xliii, 1604-1606.

The treatment of simple rectal fistula by excision and suture without cutting the external sphincter muscle. *Med. News*, N. Y., 1904, lxxxv, 640.

Rubber cushions for general surgical gynecological and obstetrical use. *Med. News*, N. Y., 1904, lxxxiv, 699-700.

Verletzungen des Rectums bei gynäkologischen Untersuchungen. *Berl. klin.-therap. Wchnschr.*, 1904, i, 775-778.

Also: *Wien klin.-therap. Wchnschr.*, 1904, xi, 775-778.

1905

Kelly, H. A. & Hurdon, E. The vermiform appendix and its diseases. Phila., 1905. W. B. Saunders & Co. 848 p. 3 pl. roy. 8°.

The great opportunity of the physician and the nurse. An address delivered at a service for physicians and nurses, Nov. 19, 1905, N. Y. 1905, Loizeaux Bros., 15 p., 32°.

The uterine curette. *Am. J. Obst.*, N. Y., 1905, ii, 662.

The treatment of the nonmalignant strictures of the rectum. *Am. Med.*, Phila., 1905, x, 479-480.

Some surgical notes on tuberculosis of the kidney. *Brit. Gynec.*, J., Lond., 1905, xxi, 130-153.

Also: *Brit. M. J.*, Lond., 1905, i, 1319-1323.

Also: *Lancet*, Lond., 1905, i, 1630-1632.

Also: *Med. Press & Circ.*, Lond., 1905, n. s., lxxix, 663-668.

The surgical treatment of renal tuberculosis. *Dominion M. Month.*, Toronto, 1905, xxiv, 125-132.

What is the right attitude of the medical profession toward the social evil? *J. Am. M. Ass.*, Chicago, 1905, xlii, 679-681.

The best way to treat the social evil. *Med. News*, N. Y., 1905, lxxxvi, 1157-1163.

The treatment of pyelitis. *Med. Rec.*, N. Y., 1905, lxxvii, 521-524.

Professor Smith on the Jersey mosquito. (*Proc. Johns Hopkins Hosp. Med. Soc.*, Nov. 21, 1904.) *Johns Hopkins Hosp. Bull.*, Balt., 1905, xvi, 115-116.

1906

Operative gynecology. 2. ed. revised and enlarged. 2. v. N. Y. & Lond., 1906. D. Appleton & Co. 680 p. 5 pl. 656 p. 17 pl. 8°.

Walter Reed and yellow fever. N. Y., 1906. McClure, Phillips & Co. 298 p. 12 pl. 12°.

The treatment of cystitis. *Canada Lancet*, Toronto, 1905-6, xxxix, 385-398.

Also: *Maritime M. News*, Halifax, 1905, xvii, 445; 1906, xviii, 17.

Also: *Canad. J. M. & S.*, Toronto, 1906, xix, 67-82.

Also: *Canad. Prac. & Rev.*, Toronto, 1906, xxxi, 61-75.

Also: *Old Dominion M. Month.*, Toronto, 1906, xxvi, 1-16.

The aseptic removal of an infected fibroid uterus. *Am. J. Obst.*, N. Y., 1906, liii, 493.

The use of a steel comb for dissection in the axilla. *Ann. Surg.*, Phila., 1906, xlii, 104-105.

Two cases of stricture of the ureter; two cases of hydronephrotic renal pelvis successfully treated by plication. *Johns Hopkins Hosp. Bull.*, Balt., 1906, xvii, 173-175.

The regulation of prostitution. *J. Am. M. Ass.*, Chicago, 1906, xlii, 397-401.

Resections of the bladder in rebellious cystitis. *N. York State J. M.*, N. Y., 1906, vi, 145-148.

Starvation and locking the bowels for from ten days to two weeks in complete tear cases. *Tr. South. Surg. & Gynec. Ass.*, 1905, Phila., 1906, xviii, 95-107.

Also: *Surg. Gynec. & Obst.*, Chicago, 1906, ii, 179-181.

The suprapubic route in operating for vesical fistulae. *Tr. Am. Gynec. Soc.*, Phila., 1906, xxxi, 225-253.

In memoriam. Arthur Weir Johnstone, M. D. (1853-1895). *Tr. Am. Gynec. Soc.*, 1906, xxxi, 427-430.

Some lessons from the life of Major Walter Reed. *Med. Libr. & Hist. J.*, Brooklyn, 1906, iv, 332-338.

A satisfactory vesical evacuator. *Surg. Gynec. & Obst.*, Chicago, 1906, iii, 330.

1907

Walter Reed and yellow fever. 2. ed. N. Y., 1907. McClure, Phillips & Co., 310 p., 12°.

Kelly, H. A., & Noble, C. P., eds. Gynecology and abdominal surgery. Vol. 1. Phila. & Lond., 1907, W. B. Saunders Co. 859 p., 8°.

Byron Robinson and his work. *Am. M. Compend.*, Toledo, 1907, xxiii, 3-4.

Success in life. *Jeffersonian*, Phila., 1906-7, viii, 86-98.

A gynecological clinic—A case of stricture of the ureter due to stone, causing severe attacks of colicky pain and finally demanding operative interference; the removal of the kidney. *Am. J. Clin. M.*, Chicago, 1907, xiv, 737-740.

The protection of the innocent. *Am. J. Obst.*, N. Y., 1907, iv, 477-481.

Remarks on dermatographic tracings in clinical demonstrations. *Internat. J. Surg.*, N. Y., 1907, xx, 188.

On a method of preserving outlines of visceral lesions on nainsook or Suisse material. *Johns Hopkins Hosp. Bull.*, Balt., 1907, xviii, 120-122.

Bimanual vibratory palpation. *J. Am. M. Ass.*, Chicago, 1907, xlviii, 1841.

Mensuration in urinary diseases. *Tr. Am. Gynec. Soc.*, Phila., 1907, xxiii, 302-346.

Surgical treatment of tuberculosis of the kidney. *Surg. Gynec. & Obst.*, Chicago, 1907, iv, 257-262.

The lesson of little things: the conquest of yellow fever. *Youth's Companion*, Bost., 1907, lxxxi, 15.

1908

Medical gynecology. N. Y., 1908. D. Appleton & Co. 676 p. 8°.

Kelly, H. A., and Noble, C. P., eds. Gynecology and abdominal surgery. Vol. 11. Phila. & Lond., 1908, W. B. Saunders Co., 862 p., 8°.

Anuria and nephrostomy by the ureter. *Johns Hopkins Hosp. Bull.*, Balt., 1908, xix, 48.

The barred road to anatomy. *Ibid.*, 196-201.

Art applied to medicine and surgery. [Illustrated.] *Tr. South. Surg. & Gynec. Ass.*, 1907, N. Orleans, 1908, xx, 1-18.

My faith. *Appleton's Mag.*, N. Y., 1908, xi, 722-724.

Out of uncertainty and doubt, into faith. (Leaflet.) [An abridgement of "My faith."]

A personal testimony. (Leaflet.) [An abridgement of "My faith."]

On Bible study. A letter to a friend. *Our Hope*, N. Y., 1908 (October).

James Carroll, 1854-1907. *Proc. Wash. Acad. Sc.*, 1908, x, 204-207.

Kelly, H. A. [et al.]. James Carroll, M. D. U. S. A., 1854-1907. *Johns Hopkins Hosp. Bull.*, Balt., 1908, xix, 1-12.

1909

Appendicitis and other diseases of the vermiform appendix. Phila. & Lond., 1909, J. B. Lippincott Co. 502 p. 8°.

Kelly, H. A., & Cullen, T. S. *Myomata of the uterus*. Phila., 1909. W. B. Saunders Co. 723 p. 8°.

Frère Jacques. *Aesculapian*, N. Y., 1908-9, i, 145-151.

Amputation of the uterus in the corpus to preserve the menstrual function. *Am. J. Obst.*, N. Y., 1909, lix, 570-581.

Also: *Tr. Am. Gynec. Soc.*, Phila., 1909, xxxiv, 536-549.

The fat appendix. *Ann. Surg.*, Phila., 1909, i, 474-476.

Post-operative psychoses. *Surg. Gynec. & Obst.*, Chicago, 1909, ix, 515-521.

Also: *Tr. Am. Gynec. Soc.*, Phila., 1909, xxxiv, 426-455.

Also: *Am. J. Obst.*, N. Y., 1909, lix, 1035-1037.

McDowell's successors in America. *Tr. Am. Gynec. Soc.*, Phila., 1909, xxxiv, 592-599.

1910

Treatment of an anteuterine pelvic abscess by sequestration and drainage. *Am. J. Obst.*, N. Y., 1910, lxi, 921-925.

An operation for umbilical hernia. *Ann. Surg.*, Phila., 1910, li, 694-696.

A chart to aid in the treatment of cystitis by distentions of the bladder. *Ann. Surg.*, Phila., 1910, lii, 664-667.

Transurethral operations in women. *J. Am. M. Ass.*, Chicago, 1910, liv, 1606-1607.

Oral prophylaxis. *Dominion Dent. J.*, Toronto, 1910, xxii, 563-570.

Suspensio uteri. *Klin.-therap. Wehnschr.*, Berl., 1910, xvii, 916-918.

The ebb and flow of hypnotism since 1660. *Maryland M. J.*, Balt., 1910, lii, 81-97.

Social diseases and their prevention. *Social Dis.*, N. Y., 1910, i, No. 3, 12-25.

The gynecological examination and topical treatment.

In: *Stereo-Clinic*, Troy, N. Y., 1910, Sect. i, 2-38, 24 stereos.

Removal of a dermoid cyst of the ovary. *Ibid.*, Sect. iii, 2-11, 7 stereos.

Vaginal incision and drainage for pelvic abscess. *Ibid.*, Sect. iii, 2-17, 12 stereos.

Abdominal hysterectomy for a fibroid uterus. *Ibid.*, Sect. iv, 2-42, 25 stereos.

Bisection for the removal of a large dermoid cyst. *Ibid.*, Sect. v, 2-48, 4 stereos.

The relaxed vaginal outlet. *Ibid.*, Sect. vi, 2-64, 49 stereos.

Examining and recording a pelvic or other abdominal tumor. *Ibid.*, Sect. vii, 2-14, 9 stereos.

Dilatation and curettage. *Ibid.*, Sect. vii, 2-28, 15 stereos.

Removal of the vermiform appendix. *Ibid.*, Sect. ix, 2-26, 18 stereos.

Closing incisions in the renal pelvis. *Surg. Gynec. & Obst.*, Chicago, 1910, xi, 201-202.

Excision of the fat of the abdominal wall; lipectomy. *Surg. Gynec. & Obst.*, Chicago, 1910, x, 229-231.

Movable kidney and neurasthenia. *Tr. Am. Surg. Ass.*, Phila., 1910, xxviii, 513-524.

Incisions in the abdominal wall to expose the kidney; incisions in the kidney to explore its pelvis. *Tr. South. Surg. & Gynec. Ass.*, 1909, [Phila.], 1910, xxii, 294-306.

Operations for hydronephrosis. *Tr. Am. Urol. Ass.*, 1909, Brookline, 1910, iii, 377-395.

A physician's view of Christ's miracles. *Sunday School Times*, Phila., 1910, lii, 133.

Bible readers and Bible perusers. *Bible Student and Teacher*, N. Y., 1910, xiii, 11-13.

Two great questions addressed to every man and the Bible answers. *Bible Student and Teacher*, N. Y., 1910, xiii, 266-268.

Some opening verses in Luke. *Bible Record*, N. Y., 1910, vii, 229-230.

1911

Pyuria. *Am. J. Surg.*, N. Y., 1911, xxv, 1-5.

The abdominal incision—the removal of the wedge of skin and fat to facilitate intra-abdominal operations. *Ann. Surg.*, Phila., 1911, liii, 364-366.

Graduated dilatation of the uretero-vesical orifice and the ureter above it. *Canad. M. Ass. J.*, 1911, n. s., i, 849-858.

Abdominal pain. *Interstate M. J.*, St. Louis, 1911, xviii, 194-196.

A new and simple method of removing a renal calculus. *J. Am. M. Ass.*, Chicago, 1911, lviii, 19-20.

Some American medical botanists. *J. Am. M. Ass.*, Chicago, 1911, lviii, 437-441.

Also: *Bull. Soc. N. Hist.*, Chicago, 1911-12, i, 1-14.

Carcinoma of the clitoris.

In: *Stereo-Clinic*, Troy, N. Y., 1911, Sect. xx, 2-10, 8 stereos.

Hæmatoma of the vulva. *Ibid.*, Sect. xx, 2-7, 5 stereos.

Removal of cyst of Bartholin's gland. *Ibid.*, Sect. xx, 2-8, 4 stereos.

The best method of exposing the interior of the bladder in suprapubic operations. *Surg. Gynec. & Obst.*, Chicago, 1911, xii, 30-33.

Also: *Tr. South. Surg. & Gynec. Ass.*, Nashville, 1911, xxiii, 64-71.

Getting up early after grave surgical operations. *Surg. Gynec. & Obst.*, Chicago, 1911, xiii, 78-79.

Boys, are you trying for the prize? *Youth's Instructor*, 1911, lix, 16 and 18.

Kelly, H. A. & Burnam, C. F. Reply to "A criticism of the technique of ureteral catheterization of Dr. Howard A. Kelly." *Am. J. Surg.*, N. Y., 1911, xxv, 220-222.

1912

Medical gynecology. 2. ed. N. Y., 1912. D. Appleton & Co. 713 p. 8°.

Walter Reed and yellow fever. Rev. ed. Balt., 1912. Med. Stand. Book Co. 329 p. 12°.

A cyclopedia of American medical biography, comprising the lives of eminent deceased physicians and surgeons from 1610-1910. Illustrated with portraits. 2 v. Phila. & Lond., 1912. W. B. Saunders Co. roy. 8°.

The treatment of incontinence of urine in women. *Therap. Gaz.* [etc.], Detroit, 1912, 3. s., xxviii, 685-687.

The history of the vesico-vaginal fistula; an address. *Tr. Am. Gynec. Soc.*, Phila., 1912, xxxvii, 3-29.

To convert sentiment into action in fighting vice. [Baltimore], 1912. 41 p. 8°.

The influence of segregation upon prostitution and upon the public. [Phila.], 1912. 15 p. 8°.

Also: *Med. Press. & Circ.*, Lond., 1912, n. s., xciv, 158-162.

Some scattered thoughts on the prostitution question and about the attitude of our judges and our police. *Social Dis.*, N. Y., 1912, No. 3, 13-34.

The social evil: what is the Church doing? *The Living Church*, 1912, 449-451 (July 27).

1913

Success in life. *Jeffersonian*, Phila., 1912-13, xiv, 1-9.

Talk on radium, delivered at the Medico-Chirurgical Faculty, April 11, 1913. *Maryland M. J.*, Balt., 1913, lvi, 151-154.

The allotment of renal and ureteral stones in shadow diagram of the body. *Old Dominion J. M. & S.*, Richmond, 1913, xvi, 229-231.

Status præsens of the prostitution question. *Tr. xv. Internat. Cong. Hyg. & Demog.*, . . . Wash. (1912), 1913, iv, 663-673.

Incontinence of urine in women. *Urol. & Cutan. Rev.*, St. Louis, 1913, xvii, 291-293.

The treatment of cancer with radium. An interview with Dr. Howard A. Kelly, of Baltimore. Reported by Burton J. Hendrick. *Am. Rev. of Rev.*, N. Y., 1913, lxviii, 722-726.

Address delivered at dedication of new building Oct. 16, 1913 [Univ. of Nebraska]. *Proc. 4. Ann. Alumni Week*, U. of N., Coll. of Med., Omaha, 1913.

Dr. Howard Kelly's appeal for Church civic service. Address at the New York Probation and Protective Association. *The Survey*, N. Y., 1913, xxx, 118-119.

Illustrated immorality. [Appeal for pictures.] (Communications.) The Survey, N. Y., 1913, xxx, 151.

Letter on Miss Eberle's white slave statuette. (Communications.) The Survey, N. Y., 1913, xxx, 312.

Commercialized vice must go. N. American, Phila., 1913 (Feb. 15).

Kelly, H. A. & Lewis, R. M. Skiagraphic demonstration of vesical tumors. Surg. Gynec. & Obst., Chicago, 1913, xvi, 308-312.

Kelly, H. A. & Lewis, R. M. Silver iodine emulsion; a new medium for skiagraphy of the urinary tract. *Ibid.*, 707-708.

Kelly, H. A. & Neel, J. C. Carcinoma of the cervix of the uterus. Johns Hopkins Hosp. Bull., Balt., 1913, xxiv, 231-242.

Kelly, H. A. & Neel, J. C. Cauterization of "inoperable" carcinoma of the cervix of the uterus. Johns Hopkins Hosp. Bull., Balt., 1913, xxiv, 372-375.

1914

Some American medical botanists commemorated in our botanical nomenclature. Troy, N. Y., 1914. The Southworth Co. 215 p. 8.

Kelly, H. A. & Burnam, C. F. Diseases of the kidneys, ureters and bladder, with special reference to the diseases in women. 2 v. N. Y. & Lond., 1914. D. Appleton & Co. 582 p. 652 p. 8°.

What radium can do. Internat. Clin., Phila., 1914, 24. s., iv, 41-43.

Radium in surgery. South. Calif. Pract., Los Angeles, 1914, xxix, 31-34.

The treatment of vesical fistulae at the vaginal vault following surgical operations. Tr. South. Surg. & Gynec. Ass., 1913, Atlanta, 1914, xxvi, 93-99.

A wonderful surgeon. [Theodor Kocher.] Am. Mag., N. Y., 1914, lxxvii, 59.

Smo and Drin—an Allegory. Union Signal, Evanston, Ill., 1914, xl, 5 and 7.

Kelly, H. A. & Burnam, C. F. Radium in the treatment of uterine hemorrhage and fibroid tumors. J. Am. M. Ass., Chicago, 1914, lxxii, 622-628.

Kelly, H. A. & Dumm, W. M. Urinary incontinence in women, without manifest injury to the bladder; a report of cases. Surg. Gynec. & Obst., Chicago, 1914, xviii, 444-450.

Kelly, H. A. & Lewis, R. M. Diagnosis of the particular forms of hydronephrosis due to movable kidney. Surg. Gynec. & Obst., Chicago, 1914, xix, 601-603.

1915

Suspension of the kidney. Troy, N. Y., 1915, The Southworth Co., 21 p. 4°.

In: Stereo-Clinic, Sect. xxix.

History of retr displacements of the uterus. Surg. Gynec. & Obst., Chicago, 1915, xx, 598-599.

The treatment of cancer by radium. Maryland M. J., Balt., 1915, lviii, 161-163.

The radium treatment of fibroid tumors. Tr. South. Surg. & Gynec. Ass., 1914, Asheville, 1915, xxvii, 230-235.
Also: Surg. Gynec. & Obst., Chicago, 1915, xx, 271-273.

Auto touring for civic righteousness. Christian Advocate, N. Y., 1915, xc, 712-713.

The virgin birth. Our Hope, N. Y., 1915 (October).

Kelly, H. A. & Burnam, C. F. Radium in the treatment of carcinomas of the cervix uteri and vagina. J. Am. M. Ass., Chicago, 1915, lxx, 1874-1878.

Also: Radium, Pittsburgh, 1916, vi, 73-82.

1916

Some radium achievements. Am. J. Surg., N. Y., 1916, xxx, 73-77.

Radium therapy in cancer of the uterus. Tr. Am. Gynec. Soc., Phila., 1916, xlii, 532-541.

Treatment of fibroid tumors with radium. Women's M. J., Cincinnati, 1916, xxvi, 1-3.

Radiotherapy. Tr. M. Ass., Alabama, 1916.

The double shame of Baltimore, her unpublished vice report, her indifference. Delaware State M. J., Wilmington, 1916, vii, 2-5.

Also: Reprinted for wider circulation by Howard A. Kelly, M. D.

A surgeon's view of Billy Sunday, Surgeon. Sunday School Times, Phila., 1916, lviii, 249.

Baker, E. C. Victims . . . ; with an introd. by Howard A. Kelly. Balt., 1916. 20 p. 8°.

Kelly, H. A. & Burnam, C. F. A résumé of results in the radium treatment of three hundred and forty-seven cases of cancer of the uterus and vagina. Am. J. Obst., N. Y., 1916, lxxiv, 326.

Kelly, H. A. & Neill, W. Cauterization and fulguration of bladder tumors. J. Am. M. Ass., Chicago, 1916, lxxvi, 721-723.

1917

Methods and results of radium treatment of uterine hemorrhage due to other causes than malignancy. Tr. Am. Gynec. Soc., Phila., 1917, xliii, 408-423.

Also: Am. J. Obst., N. Y., 1917, lxxvii, 513.

1918

Fibroid tumors of the uterus treated with radium. Charlotte [N. C.] M. J., 1918, lxxvii 135-137.

John R. Young, pioneer American physiologist. Johns Hopkins Hosp. Bull., Balt., 1918, xxix, 186-191.

Fibroid tumors and radium. Virginia M. Month., Richmond, 1918, xlv, 1-3.

Two hundred and ten fibroid tumors treated by radium. Surg. Gynec. & Obst., Chicago, 1918, xxvii, 402-409.

Also: Tr. Am. Gynec. Soc., Phila., 1918, xliiii, 317-335.

Theodore Caldwell Janeway, 1872-1917. Boston M. & S. J., 1918, clxxx, 597-599.

Joseph Price, 1853-1911. Boston M. & S. J., 1918, clxxx, 681-684.

John Herr Musser, 1856-1912. Boston M. & S. J., 1918, clxxx, 772.

Dr. Keen on medical research. Science, N. Y., & Lancaster, Pa., 1918, n. s., xlvii, 419.

Whiskey and the "flu." Manufacturers Record, 1918, lxxiv, 72a.

A message to my three boys who have enlisted. The Evangelical, 1918, 8-9 (January 2).

When a nation prays then victory will come. The Evangelical, 1918 (February 6).

How radium's rays point to Christ. When nature speaks in a sparkling parable. The Sunday School Times, 1918, 109 (February 23).

1919

American medical biography. Balt., 1919, Norman, Remington Co. [In Press.]

The treatment of papillary tumors of the bladder in women. Am. J. Obst., N. Y., 1919, lxxx, 328-335.

Reginald Heber Fitz, 1843-1913. Boston M. & S. J., 1919, clxxx, 75-77.

The treatment of uterine hemorrhages from the modern viewpoint. Therap. Gaz., Detroit, 1919, xliiii, 229-233.

Dilatation and curettement. Therap. Gaz., Detroit, 1919, xliiii, 305-314.

The early recognition and treatment of cancer—the duty and the opportunity of the general practitioner. Therap. Gaz., Detroit, 1919, xliiii, 381-389.

Mushrooms and toadstools. Therap. Gaz., Detroit, 1919, xliiii, 465-478.

Cancer of the uterus. Therap. Gaz., Detroit, 1919, xliiii, 611-621.

A tribute to Sir William Osler. South. M. J., Birmingham, Ala., 1919, xli, 346-347.

Osler as I knew him in Philadelphia and in the Hopkins. Johns Hopkins Hosp. Bull., Balt., 1919, xxx, 215-216.

Address delivered before the World's Conference of Anti-Saloon League Workers, Washington, D. C., June 4, 1919. Balt., 1919, Anti-Saloon League of Maryland, 12 p. 16°.

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On Bible study. New York, n. d., Loizeaux Bros., 14 p. 32°.

Then and now. New York, n. d., Loizeaux Bros., 8 p. 12°.

The Sabbath and the body. Educational campaign for Sunday Schools and young people's societies. Lesson 2. Philadelphia Sabbath Association.

On Bible study. Daily Bible leaflet No. 3. World's Morning Watch, Clifton-Springs, N. Y.

What a great doctor says. American Sunday School Union, Phila. In favor of votes for women. Testimonio personal.

Many articles by Dr. Kelly signed "H. A. K." appear regularly in the *Christian Citizen*.

CHRONIC PEMPHIGUS VEGETANS OF SEVERAL YEARS' DURATION

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Though pemphigus vegetans is described as terminating fatally usually within one year from onset, a few cases of long duration are known, notably one recorded by Neumann of ten years' duration and another of similar duration described by Köbner in 1894. We have recently had under observation, in the private ward of this hospital, a patient who has already suffered from the disease for more than five years and who is still living, the condition exhibiting remarkable remissions and exacerbations. The malady is so rare and its nature is so obscure that even single cases that deviate in any way from the ordinary type should be recorded in the hope that data may gradually be accumulated that will clear up the mystery that still enshrouds the disease.

Pemphigus vegetans was clearly differentiated and first described as a clinical entity by Neumann¹ in 1886. The first English case to be reported was the well-known one of Crocker² (1889). In 1891 Hyde³ described the first case recognized in America. A fatal case from our clinic was reported with careful clinical history, autopsy findings, together with histological and bacteriological examinations, in 1903, by Hamburger and Rubel.⁴ They reviewed the literature thoroughly and showed the gradual differentiation of the diseases once grouped together as "pemphigus." No review of the development of our knowledge of the disease is included, therefore, in the present paper.

PERSONAL OBSERVATIONS

The case to be reported here is that of a young, unmarried woman, age 20, born in the United States, who was admitted to the medical service of the private wards, Johns Hopkins Hospital, on July 2, 1917. She complained of a "skin eruption" and of "colitis."

The family history was negative. One paternal aunt had died of cancer. There was no history of any skin disease in the family.

As to her own past history, the patient had never been robust. She had the usual diseases of childhood without complications. At the age of three years, she suffered from "intestinal indigestion" and a diagnosis of "follicular colitis" was made; and at the age of six, she is said to have had a similar attack, during which she had abdominal pain, "indigestion," diarrhea, and blood in the stools. Whenever she has been "run-down," from childhood on, she has had somewhat similar intestinal attacks. For some time past, she has had a chronic conjunctivitis and blepharitis. Her habits and mode of life have been normal. She has made a practice of sleeping out-of-doors.

About six years prior to admission the patient lived for a time in Constantinople. While there she had digestive disturbances, and on the way home to the United States a most distressing "urticaria" developed. Somewhat later she was "covered with an eruption much like that present at the time of admission."

There has been some intestinal trouble ever since her trip abroad. Thus, in 1913, the patient was seriously ill for some time with "colitis." In 1914, an appendectomy was performed, followed by general improvement. In August, 1915, lesions appeared in the mouth; in November, 1915, the eyes became inflamed and in December of the same year lesions reappeared in the mouth and also made their appearance on the external genitals (vulva) for the first time. A diagnosis of "herpes" was made at this time; but, later on, the opinion was that the lesions were luetic in origin and the patient received numerous intravenous injections of salvarsan. In August, 1916, another physician made the diagnosis of "neurotic herpes," but he also soon changed his opinion and made the diagnosis of syphilis, treating the patient accordingly. There was some improvement following this arsenical treatment. In October, 1916, the lesions, which were described as "superficial ulcerations developing after small blisters had burst," reappeared in the mouth and about the vulva. Another series of intravenous injections was administered and five weeks later the lesions had disappeared. In December, 1916, ulcerative lesions again appeared in the mouth. In April of the following year, 1917, lesions in the throat were troublesome and those on the vulva were also noticeable, but were

¹ Neumann: Vierteljahrsschrift für Dermatol. u. Syph., Wien, 1886, p. 159.

² Crocker: Brit. M. J., 1889, I.

³ Hyde, J. N.: J. Cutan. Dis., 1891, IX, 412-456.

⁴ Hamburger, L. P., and Rubel, M.: Bull. Johns Hopkins Hosp., 1903, XIV, 63-70.



FIG. 1.—Pomphigus vegetans. The appearance of the axillary lesions on January 6, 1918, is here shown.



not pronounced until May when the severe attack that led the patient to apply for treatment at this hospital began.

Physical Examination.—At the time of admission, the physical examination showed a marked degree of emaciation, the patient being 36 pounds below her calculated ideal weight. There was slight pallor of the skin and mucous membranes. The eyes showed a slight conjunctivitis and a moderate degree of blepharitis. On the lips, palate and pharynx there was extensive superficial ulceration, which, over the lips, had involved the adjoining skin and had gone on to crust formation. The examination of the genitalia showed extensive excoriations of the labia majora, labia minora and vaginal mucosa. The labial lesions varied in size, all the way from small isolated vesicles to areas 1.5 to 2 cm. in diameter. The edges of the larger lesions were definitely elevated and consisted of closely set vesicles containing turbid fluid. The lesions were covered with a foul, mucoid discharge. The inflammatory areola about the lesions was slight. There was no general glandular enlargement and the spleen was not palpable. The remainder of the physical examination showed no significant abnormality. The temperature was 99.6° F. and the pulse-rate 90. The patient complained much of pain in the region of the vulva and in the throat. She could not eat and was rapidly losing weight.

Laboratory Examinations.—At the time of admission (July, 1917) the blood examination showed: Hemoglobin 60 per cent (Sahli), and 15,800 leucocytes. An examination made a month later showed R. B. C., 4,600,000; W. B. C., 8400; Hb. (Sahli), 81 per cent. In February, the examination showed R. B. C., 4,500,000; W. B. C., 8200; Hb. (Sahli), 88 per cent; and in the differential count PM. N., 68 per cent; PM. B., 0.0 per cent; PM. E., 1.5 per cent; S. M., 18 per cent; L. M., 12 per cent; Trans., 1.5 per cent.

The examination of the stools chemically and microscopically was negative.

The urine on a number of examinations was normal, except for the presence, occasionally, of a trace of albumin.

The Wassermann test of the blood-serum was negative on two occasions, as it had previously always been.

A culture for bacteria, made from the mouth lesions, showed no unusual organisms, though colonies, chiefly of *Staphylococcus aureus*, grew out. Smears made from the lips, mucous membrane of the cheeks and pharyngeal pillars were all quite similar, showing only a few cocci and bacilli. There was nothing suggestive of the organisms that are found in Vincent's angina; there were no bacilli that resembled *B. diphtheria*, nor were any pathogenic moulds found.

Röntgenograms of the gastrointestinal tract showed a large, ptosed, cowhorn-shaped stomach, which was drawn well over to the right and downward. There was sluggish peristalsis and delayed emptying time. There were, however, no filling defects. There was some cecal stasis, enteroptosis and evidence of (post-operative?) adhesions in the lower right quadrant.

Nose and Throat Report.—An examination made by Dr. S. J. Crowe on July 6 showed moderate enlargement of the posterior cervical lymph glands and superficial ulceration of

the soft palate, of both tonsils, pharynx and cheeks. The larynx and naso-pharynx were not involved in the ulcerative process. The paranasal sinuses showed no evidence of infection.

Neurological and Psychic Examination.—There were no objective disturbances of sensation, and subjectively only pain and some itching were complained of. Motility and reflexes were normal. Psychically, the patient reacted normally in periods of remission, though during periods of exacerbation she was depressed, irritable and capricious.

Protein-Sensitization Tests.—In order to rule out, if possible, all the ordinary proteins (foods, pollens, etc.) that act as causes of allergic states, cutaneous tests were made with egg, cocoa, casein, peas, barley, wheat (bread), potato, golden-rod pollen, rag-weed pollen, timothy pollen, horse-dander, and staphylococci. The results were all negative.

Course in the Hospital.—About three weeks after admission the patient developed an outspoken diarrhea. At this time a considerable amount of mucus and several large blood-clots were found in the stools. Microscopically, there were numerous leucocytes, fatty acid crystals, neutral fat and some muscle fibers in the feces. Cultures of the stool and of the washed mucus showed only the colon bacillus. Because many of the stools were large, light-colored and pulsatious, a quantitative diastase determination was made. The quantity present was above the normal minimum.

Throughout the patient's stay in the hospital, the diarrhea and intestinal symptoms, the colicky pains, the vague abdominal distress and the "indigestion" were the most distressing symptoms, causing more trouble at most times than the skin lesions. There were seldom less than three, and often as many as ten, stools a day. Occasionally, there were attacks of vomiting, the vomitus being at times blood-tinged.

By the first of August the lesions in the mouth had disappeared and those about the vulva were much improved. On this date groups of several small vesicles were seen on the hard palate. The fluid was clear and small in amount. Each vesicle was surrounded by a slight erythematous areola. The vesicles did not persist for more than 24 hours and, after rupturing, coalesced to form very superficial ulcers varying in size from .25 to 1.5 cm. in diameter. The ulcers were grayish-white in color and seemed to be covered with a pellicle, the surrounding areola was slight. At this stage, the resemblance to the mucous patches of syphilis was striking.

Ten days after the reappearance of those in the mouth two symmetrical lesions developed on the breasts. These attained the size of a quarter and resembled closely the lesions of the vulva, except that there was more inflammatory reaction about them and less discharge from the surface. They persisted for three weeks, disappeared spontaneously and left no scars.

About the time of the development of the breast lesions the patient's temperature became elevated, reaching 102.6° F. It subsided within 48 hours. This was the only febrile episode of moment. A blood culture made at this time showed no growth. No adequate explanation of the fever was arrived at.

About the last of August, 1917, there developed pain on defecation and the amount of blood and mucus in the stools increased. A proctoscopic examination at this time showed a superficial ulcerated area, rather dark blue in color; it covered the entire circumference of the rectum and extended upward about four inches, where it merged with mucosa of normal appearance. Ten days later the appearance of the rectal mucosa was again normal.

During September, October and the first half of November, the patient was somewhat better. The lesions recurred from time to time in the mouth, but were transient. There were brief attacks of diarrhea, but the abdominal pain was less disturbing than it had been.

About the third week in November, extensive ulceration again occurred in the mouth; the lesions about the vulva, which had almost cleared up, became more extensive and painful; several small lesions appeared in the left axilla; the diarrhea became more intractable. The body-weight which had increased from 107½ pounds to 129½ pounds began, at this time, to decrease, and the patient lost steadily up to the time of her discharge from the hospital.

The axillary lesions appeared first as groups of small vesicles. They ruptured, coalesced and formed very superficial ulcers. At no time were any true bullæ seen.

The lesions on the vulva and in the axilla progressed steadily and the condition of the axilla on January 6 is shown in Fig. 1 (colored drawing). Fig. 2 (a photograph) shows the appearance of the vulval lesions on January 21, 1918.

During February, 1918, the axillary lesions spread, covering the entire axilla and extending down the thoracic wall for several centimeters. The perigenital lesions spread, extending over the mons veneris and down the thighs for a short distance. As the lesions progressed, the granulomatous and vegetative character became more evident. The edges were definitely elevated and had a "rolled" appearance. The secretion from the large lesions was abundant, foul, yellowish in color and mucoid. A number of small lesions now appeared over the face, abdomen and buttocks, but they were of short duration.

Two weeks before discharge from the hospital, which was on March 12, 1918, a distinct improvement in the condition of the lesions had set in. They no longer increased in size, were less elevated and there was less discharge from them. The diarrhea continued, however, to be troublesome. The body-weight was 112½ pounds, only five pounds more than on admission.

Subsequent Course.—Upon discharge from the hospital, the patient returned to the care of Dr. J. A. Fordyce, under whom she had previously been for a time. He has kindly supplied us with the following information:

For three or four weeks she seemed very much better, but about May 1, 1918, she became decidedly worse again. There was an extensive outbreak of lesions about the vulva, thighs and lower part of the abdomen. About the middle of May, lesions appeared over the scalp, neck, back and chest and intractable diarrhea again developed.

When seen by one of us on June 1, 1918, the patient's condition appeared to be worse than at any time previous. There was marked pallor and emaciation; the lesions were more extensive than ever and the process appeared to be very active.

Later she improved somewhat, and left New York City for her home. On September 25, 1918, the patient's mother wrote:

She has not suffered so acutely as she did from the attack she had in New York, but the trouble never clears up and now the outbreak is more extensive than ever before. Twice her head has been entirely free from the eruption, and then it has broken out again; now it is clearing for the third time. She has had a great deal of digestive trouble. . . .

The patient has not been seen by us since, but in response to a note of inquiry, we learned at the end of January, 1919, that she was again having a remission, attributed this time to Christian Science. She says in her letter:

You will be glad to hear that, though I am not entirely well, I have every hope of being so, having been so far healed through Christian Science as to be able to be about and lead a normal life. When I was desperately ill last fall and no one held out any hope of my recovery, Dr. ———, an old friend of my father's, advised my turning to Christian Science. I was prejudiced against Science and was too weak at the time to be troubled, but I am firmly convinced that I was literally pulled from the brink of the grave by the power of prayer. Certainly, all medical means had been exhausted. Later, when I was still very ill, I turned to Christian Science and have since steadily improved.

Histological Study.—On January 21, 1918, a bit of the cutaneous lesion, indicated by the arrow in Fig. 2, together with some of the surrounding normal tissue was excised for histological study. The sections were stained for acid-fast organisms, for ordinary bacteria, by Gram's method, and by the Levaditi method for spirochetes. An examination of these sections failed to show any bacteria or parasites.

The following is a report on the histology by Dr. I. R. Pels, of the Department of Dermatology:

The sections are stained with hematoxylin and eosin. With the low power one sees a marked thickening and irregularity of the rete layer. The striking features of the section are the dilatation of the lymph spaces and blood-vessels, with marked infiltrations, especially about the latter, and extending in particular to the vessels deep down in the corium. In one place there is marked edema of the papillary layer, with a suggestion of beginning vesicle formation. The adnexa of the skin appear normal.

Under the high power one sees that the rete is thickened irregularly with some hyperkeratosis, acanthosis, and elongation of the rete pegs. The granular layer is increased in thickness in certain places. There is some edema of the prickly-cell layer and occasional infiltration with small mononuclear cells. The pars papillaris shows in some places a marked edema. There is dilatation of lymph-vessels and blood-vessels, and there are also many large lymph spaces. In one area the papillæ have been entirely obliterated, apparently through pressure. There is marked infiltration with mononuclear cells; these are collected particularly around blood-vessels; the infiltration, in some instances, extends to a level directly beneath the rete layer. There is some edema in the corium. There are many small blood-vessels, probably newly formed. No marked changes are to be made out in the elastic or connective-tissue fibers. The blood-vessels are enlarged, but there is no definite endarteritis to be seen. The walls of the arteries,



FIG. 2. Pimpliens vegetans. The appearance of the lesions about the vulva on January 21, 1919. The elevated, "rolled edge," of the lesions is to be noted. Sections for the histological study were made from the lesion indicated by the arrow.

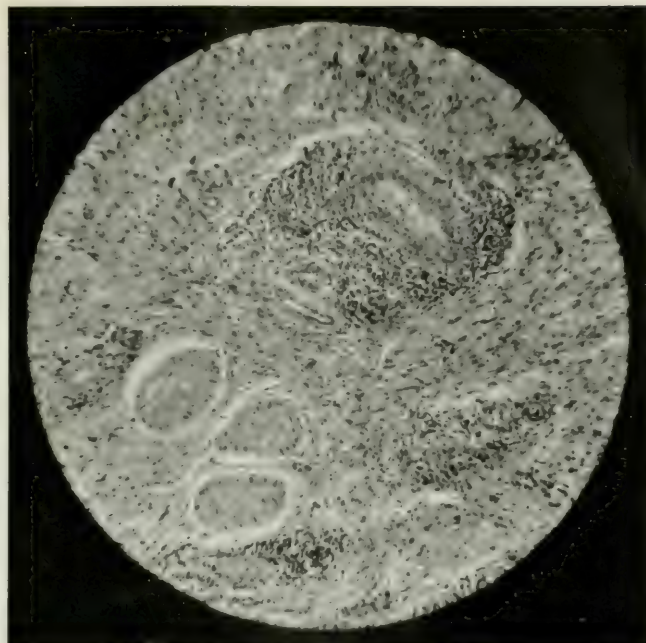
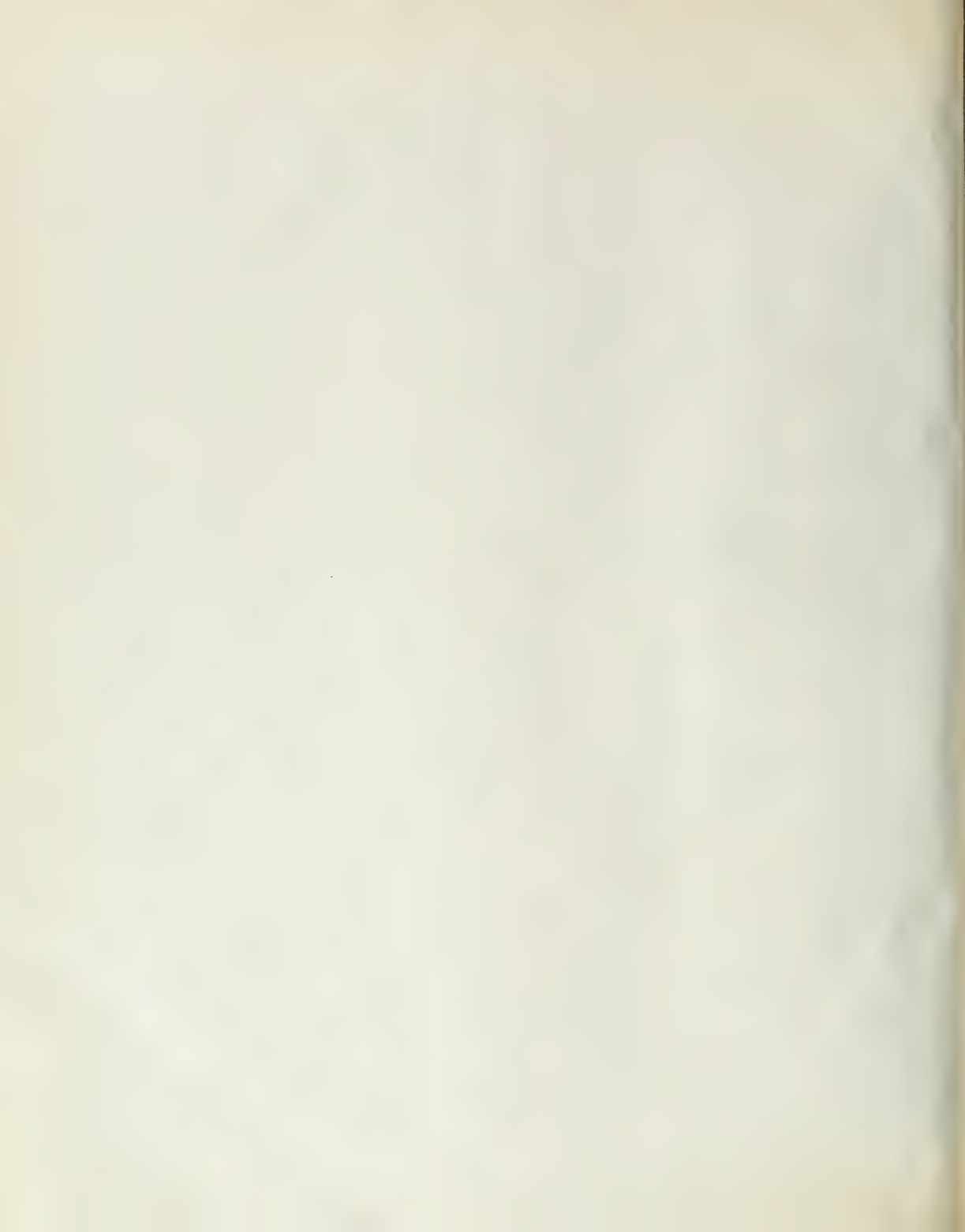


FIG. 3. Pimpliens vegetans. The characteristic small mononuclear perivascular infiltration is well shown.



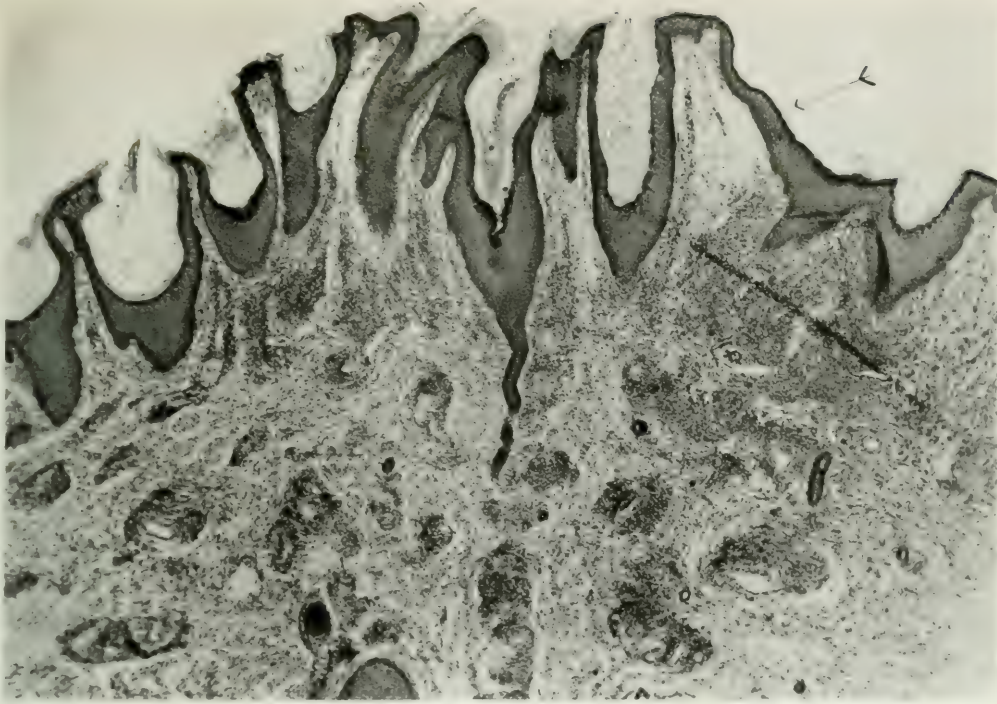


FIG. 4. Pemphigus vegetans. Photomicrograph of a characteristic portion of the lesion under high power magnification. The edema of the papillary layer is well shown in the area indicated by the arrow. The dilatation of the blood vessels with the surrounding infiltration is evident.

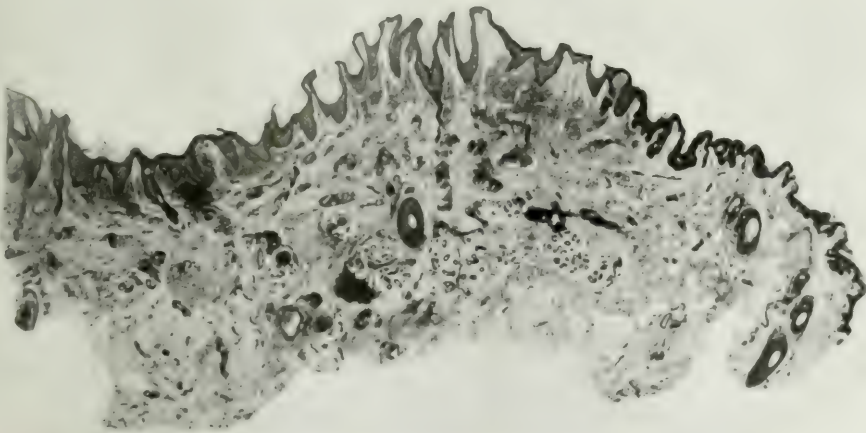
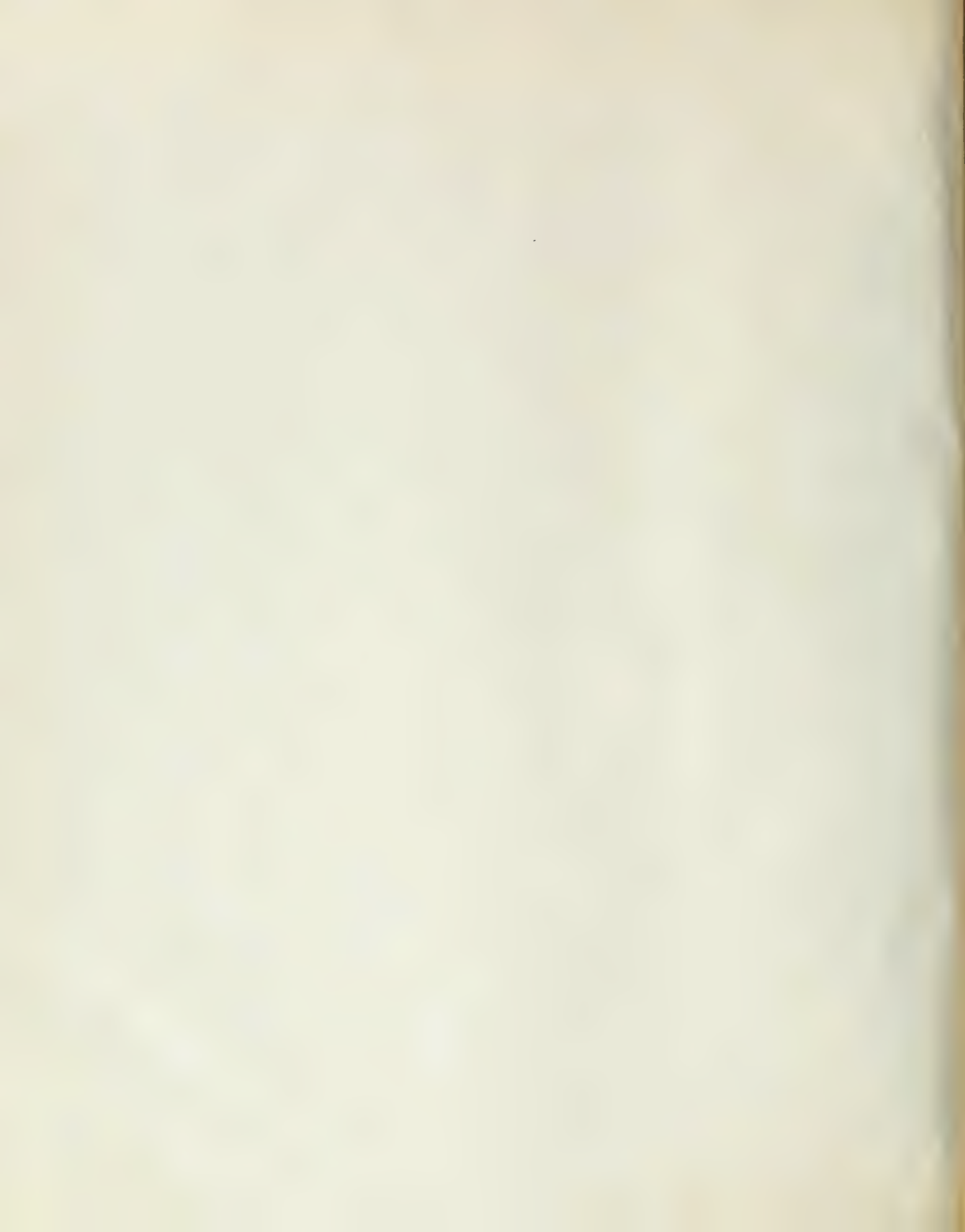


FIG. 3. Pemphigus vegetans. Photomicrograph of the entire section under low power magnification. The transition from practically normal tissue at the right to the pathological lesion should be noted. The thickening and irregularity of the rate over the edema of the papillary layer and the perivascular infiltration in the corium are evident.



however, are thickened, and there is a suggestion of occlusion of some small vessels. Many of the vessels are filled with red blood-cells and there is a marked cellular infiltration of the vessel walls and of the tissues just outside them. Even the deepest blood-vessels of the corium show a perivascular exudate of round cells.

The infiltration cells consist for the most part of small mononuclear elements, but there are a few polymorphonuclear cells, some of which have a reddish-staining protoplasm, suggesting an eosinophilic granular content. There are, also, a few plasma-cells. Mast-cells were not seen (special stain required). My impression is that we are dealing with an inflammatory reaction, sub-acute in type, with formation of new vessels, giving rise to a granuloma. There is, on the part of the blood-vessels, apparently a reaction to some agent causing extravasation of cells with edema and subsequent enlargement and thickening of the rete layer. It is not a picture of syphilis or of tuberculosis; it corresponds more to the histologic picture of pemphigus vegetans.

Treatment.—During the patient's long stay of eight and a half months in the hospital many and various local and general measures were tried. None had any directly curative effect upon the lesions of the skin and mucous membranes.

Upon admission, the most urgent indication seemed to be to overcome the emaciation, anemia and diarrhea. With this in view, the patient was kept in bed, in charge of a special nurse, and placed upon a bland diet to which liberal amounts of milk and cream were added. Dilute hydrochloric acid, Bland's pills and various anti-diarrheal mixtures were also used. There was a steady gain in weight and improvement in the anemia until the last severe attack began shortly before she left the hospital. For the intestinal condition, yeast was tried for a while, half a cake twice a day, without any apparent effect. Later, hypodermic injections of emetine hydrochloride were given, but no improvement followed.

Locally, many different ointments, lotions and dusting powders were used; aside from alleviating the pain temporarily, they were of no value.

Several courses of sodium cacodylate, in larger and in smaller doses, were given. No definite effect upon the lesions was observed.

In November, autohemotherapy was tried, the patient receiving two injections of whole blood. This treatment had to be given up because of the patient's condition.

In January, radium (180 mgm.) was applied to the axillary lesions by Dr. Curtis Burnam for 35 minutes. There was no observable effect.

In February, two intravenous injections of arsphenamine (0.4 and 0.5 gm.) were given. Early in March the axillary lesions were twice treated with x-rays. Following the arsenical and Roentgen-ray treatments both the axillary and vulval lesions improved markedly. There was also great improvement in the patient's general condition, but six weeks later the eruption was more widespread than ever before.

Throughout the course, most benefit was derived from general upbuilding measures and, perhaps, from injections of salvarsan (or arsphenamine), though remissions and exacerbations seemed to recur quite independently of any therapy.

Discussion.—We have had, then, under our observation, over a long period, a young woman who has suffered from a

remarkable form of vesiculo-ulcerative, granulomatous process, which has involved the skin and mucous membranes, which has exhibited a marked tendency to spontaneous remissions and exacerbations, and has proved refractory to all kinds of therapy thus far employed.

That the diagnosis of chronic pemphigus vegetans is a correct one seems certain from: (1) The character of the lesions and especially their resemblance to those of syphilis (for which, as in so many cases of pemphigus vegetans, the disease was for a time mistaken); (2) the clinical course of the case; (3) the histological examination of the excised tissue; and (4) the exclusion of tuberculosis, syphilis and other common causes of granulomatous processes. In this diagnosis, Dr. J. A. Fordyce, of New York, and Dr. J. W. Lord and Dr. I. R. Pels, of Baltimore, all experienced dermatologists, concur.

Certain features, it is true, made one hesitate, at first, to make a diagnosis of pemphigus vegetans. Thus, as Dr. Fordyce pointed out, it is uncommon in pemphigus vegetans to have the lesion remain localized for so long a time to the oral mucosa and the genital organs; and, besides, the lesions seemed to be deeper than in most cases of pemphigus. For these reasons, the diagnosis of "Periadenitis mucosa necrotica recurrens" (see Sutton's Text-book) was seriously considered; but, as Dr. Fordyce emphasizes, the character and the localization of the lesions, the chronic course and the resistance to all therapeutic measures employed, confirm the diagnosis of pemphigus vegetans. Moreover, the histological study revealed a perivascular granulomatous infiltration rather than a periadenitis.

What can be the etiology of this remarkable malady? We have been unable to answer this question satisfactorily, though there are several features that have interested us especially; these may give clues to etiology and spur us on to further studies in similar cases.

Thus, in the first place, though the disease does not appear to be contagious (in the sense in which this word is ordinarily used), still there is much to make us believe that it is due to a chronic infection. Its resemblance, clinically, to syphilis, the episodic pyrexias and transitory leucocytoses that accompany it, the chronicity and resistance to therapy, the tendency of the lesions to eccentric extension, and the histological picture of a granulomatous process (similar to, but not identical with, granulomatous processes due to known infectious agents like the *Treponema pallidum* of syphilis, the *Treponema pertenue* of yaws, the *Bacillus tuberculosis*, the *Bacillus mallei*, the *E. rhinoscleromatis*, the *Bacillus lepro*, the *Streptothrix*, the *Sporotrichum schenckii*, the *Cryptococcus gluchristii* (of so-called blastomycotic dermatitis) and the *Posadasia esseri-forme* (of coccidioidal granuloma or the San Joaquin Valley disease), are all features that make us suspect strongly that we must be dealing with some chronic bacterial infection or possibly a fungus.

In the second place, one must be struck with the elective affinities of the disease-process for certain parts of the skin and mucous membranes. Thus, though any part of the skin

may be involved, the disease shows an especial tendency to attack the perigenital region, the inguinal regions, and the axillæ. Again, the mucous membrane most often attacked first is that of the mouth and throat, though it is not uncommon to have the vagina and the rectum also involved. In our patient, besides the rectal involvement, there had been a history of "colitis" and of severe gastrointestinal attacks from earliest life on, a point that may be of some importance. Our patient suffered also from chronic conjunctivitis and blepharitis; in a case described by Ludwig (1897) the preputial sac and urethra were first affected; and in Hamburger and Rubel's case, hoarseness due to the involvement of the laryngeal mucosa was the first symptom. These sites of predilection of the lesions can, of course, be no accident, and we shall doubtless, sometime, find an explanation of them.

In the third place, we lay a good deal of stress upon the fact

that, in the lesions, *the infiltration of the tissues with small mononuclear cells is predominantly perivascular*. The chemotactic influence, exerted upon the small mononuclear elements (and to a slight extent upon the polymorphonuclear elements), is chiefly localized (in the corium of the affected areas of skin) in the immediate neighborhood of the blood-vessels. Though this does not prove that the causative microorganisms are similarly situated, the fact is suggestive.

In the fourth place, *the occurrence of marked exacerbations and remissions in the course of the disease presents a striking analogy with what we know of recrudescences and ameliorations in some of the treponemal diseases, especially syphilis and yaws*. Though analogies of this sort are not to be taken too seriously, we must, in a grave disease like pemphigus vegetans, pay close attention even to straws, in the hope that they may show us which way the wind blows.

STUDIES ON BLOOD SUGAR

IV. EFFECTS UPON THE BLOOD SUGAR OF THE REPEATED INGESTION OF GLUCOSE

LOUIS HAMMAN and I. I. HIRSCHMAN

In a previous communication the authors¹ have demonstrated the blood sugar response to the ingestion of a single large dose of glucose in normal persons and in others suffering from various diseases. For this study 100 grams of glucose were administered in the early morning after the night fast and the blood sugar and urine sugar estimated at short intervals thereafter. It was demonstrated that there are two important types of reaction, the normal type and the diabetic type, and still a third type, not nearly so clearly distinguished as these two, the reaction of increased carbohydrate tolerance. Although the reaction in normal persons varies in different individuals and in the same individual under different circumstances, its general characters are as follows: the blood sugar rises rapidly, but seldom exceeds 0.15 per cent; it falls somewhat more slowly to the original level, the whole reaction being over in less than two hours. In diabetics the rise is higher and longer sustained. If the blood sugar surpasses 0.18 per cent, sugar usually appears in the urine, but sometimes it appears at a somewhat lower level and at other times it fails to appear even though 0.2 per cent of blood sugar is exceeded. From two to five hours pass before the blood sugar reaches the original fasting level. When the carbohydrate tolerance is increased, there is only an insignificant rise in the blood sugar, which has usually a low fasting level.

Epstein² and Woodyat³ have raised the objection that these variations in blood sugar following the ingestion of glucose represent not real variations in the sugar content of the blood, but apparent variations due to changing blood volume. This possibility had suggested itself to us, but the investigations of Mosenenthal and Hiller⁴ show conclusively that there is no constant relation between variations in blood-sugar percentage and the water content of the blood. Indeed, these two factors

show such bizarre relations that the one surely cannot depend entirely upon the other.

There is every possible gradation in the response to glucose ingestion, from the low insignificant curve of high glucose tolerance to the extreme and prolonged curve obtained in severe diabetes. However, the so-called diabetic curve is not peculiar to diabetes, for similar curves, though usually not so extreme, are obtained in nephritis, in hyperthyroidism and in many other conditions of lowered carbohydrate tolerance. These innumerable gradations force upon us the conviction that disturbances of carbohydrate tolerance are quantitative, not qualitative, variations. In other words, that diabetes represents functionally a disturbed, not an altered, mechanism of carbohydrate control.

For many years investigators have sought to distinguish between the glucosuria of diabetes and the glycosurias due to a great variety of other conditions. Of the many distinguishing marks that have been proposed only two⁵ are still urged as pertinent, namely, the paradoxical law of Allen and the diuretic effect of sugar in diabetes. Under normal conditions, when sugar is injected intravenously in large quantity, it acts as a diuretic; administered otherwise, it diminishes the output of urine. In diabetes sugar acts as a diuretic by whatever route it be administered. But although this distinction is true for normal and totally diabetic animals, it is only relatively true for human beings. The ease with which sugar acts as a diuretic depends upon the degree of diabetes; in mild cases conditions are much nearer the normal than in the completely diabetic. In other words, the ease with which sugar produces diuresis depends directly upon the degree of carbohydrate tolerance and it varies with this tolerance. Here again the distinction is purely quantitative and the varying diuretic

effect of sugar surely cannot be pointed out as a mark of distinction between diabetes and other glycosurias. How convincingly the observations of Woodyat and his co-workers confirm this statement! By carefully measured and timed intravenous injections of glucose the tolerance of an individual can be accurately determined and sugar begins to act as a diuretic when this limit is overstepped.

It follows, then, that the only remaining feature that can be drawn upon to point a qualitative distinction between diabetes and other glycosurias is Allen's paradoxical law. Allen enunciates this law in these words: "Whereas in normal individuals the more sugar is given the more is utilized, the reverse is true in diabetes." Apparently this law was enunciated to fit conditions in totally diabetic animals to which it applies aptly enough, but if we understand properly what is meant by the law, it is not applicable to diabetes in human beings. When carbohydrate tolerance is reduced only mildly the level of tolerance is by no means absolute. For instance, if the ingestion of 50 grams of glucose be followed by the excretion of 1 gram of glucose in the urine, the ingestion of 100 grams will not cause an excretion of 51 grams. Far from it! Such experiments have been frequently made and only a small proportion of the excess has been recovered from the urine. Only when excessive amounts of glucose are administered intravenously and at a uniform rate is the proportion of excretion constant. Here again the difference seems distinctly to be quantitative and not qualitative.

It occurred to us that further important evidence bearing upon this point could be obtained by testing the reaction of patients to the repeated ingestion of glucose. If there be a qualitative difference in the utilization of glucose by normal persons and by diabetics, such tests should certainly give evidence of the difference. The only observations upon this point that we were able to find in the literature are a few experiments upon rabbits reported by Bang. In normal rabbits Bang finds that the second administration of a certain dose of glucose given during the decline of the reaction from the first administration is followed by a much less marked reaction than was the first.

EXPERIMENTAL RESULTS

In normal persons the administration of a second dose of glucose immediately after the reaction to the first dose produces a much less marked reaction upon the blood sugar than did the first dose. The protocols of experiments I and II illustrate this.

EXPERIMENT I

E. L. C., male, single. Age: 28. Healthy physician.

Time	Blood sugar per cent	Urine c. c. per hour	Urine sugar grams per hour
8.30	0.086	0	0
Glucose: 100 grams in 300 c. c. water.			
9.00	0.118	88	0
9.30	0.110	74	0
10.30	0.087	162	0
Glucose: 100 grams in 300 c. c. water.			
11.00	0.087	150	0
11.30	0.078	150	0
12.30	0.096	111	0

Time	Blood sugar per cent	Urine c. c. per hour	Urine sugar grams per hour
Glucose: 100 grams in 300 c. c. water.			
1.00	0.080	31	0
1.30	0.087	26	0
2.30	0.094	26	0

EXPERIMENT II

B. H., male, single. Age: 29. Healthy physician. The patient, when previously tested, had shown a low renal threshold; that is, sugar had appeared in the urine when the blood sugar reached 0.14 per cent.

Time	Blood sugar per cent	Urine c. c. per hour	Urine sugar grams per hour
9.15	0.110	28	0
9.16	Glucose: 100 grams in 300 c. c. water.		
9.45	0.162	28	Trace
10.15	0.127	30	Trace
10.45	0.130	26	0
10.50	Glucose: 100 grams in 300 c. c. water.		
11.20	0.110	28	0
11.50	0.122	21	0
12.20	0.115	26	0

These experiments indicate that the mechanism of carbohydrate utilization, once stimulated, works more efficiently than when called upon abruptly to manage large amounts of glucose. Probably to this fact is largely due the better utilization of sugar slowly absorbed, and the almost unlimited power of the body to utilize starch.

In diabetics the same difference is observed as in normal persons, although the difference is not so marked. The following protocols illustrate this point:

EXPERIMENT III

A. B., male, white, married. Age: 46. Dispensary No. 46750. A moderately severe diabetic who had become sugar-free on a carbohydrate free diet.

Time	Blood sugar per cent	Urine c. c. per hour	Urine sugar grams per hour
8.25	0.161	42	0
8.30	Glucose: 20 grams in 300 c. c. water.		
9.00	0.205	51	0.3
9.32	0.244	56	1.57
10.30	0.196	45	0.9
11.30	0.180	68	0.66
11.35	Glucose: 20 grams in 300 c. c. water.		
12.05	0.161	63	0.23
12.30	0.188	55	0.26
1.30	0.205	117	0.44
2.30	0.164	113	0.34

EXPERIMENT IV

A. T., male, white, married. Age: 40. Hospital No. 37026. Diagnosis: Hypertension, myocardial insufficiency, emphysema, arterio-sclerosis, diabetes mellitus, obesity. The patient had only a small amount of sugar in the urine, easily controlled by a moderate regulation of the diet.

Time	Blood sugar per cent	Urine c. c. per hour	Urine sugar grams per hour
8.35	0.150	4	0
8.38	Glucose: 100 grams in 300 c. c. water.		
9.10	0.200	5	0
9.42	0.272	33	0.68
10.45	0.222	76	2.66
11.15	0.190	49	1.63

Time	Blood sugar per cent	Urine c. c. per hour	Urine sugar grams per hour
11.18	Glucose: 100 grams in 300 c. c. water.		
11.45	0.212	41	1.36
12.27	0.209	54	1.69
12.57	0.173	37	0.56

Persons with lowered carbohydrate tolerance but without outspoken diabetes react in a similar way. Even if the second dose of glucose be much larger than the first the reaction following is not so marked.

EXPERIMENT V

W. G., male, white, single. Age: 47. Hospital No. 36926. The patient had a mild infection of unknown cause and mental symptoms. No definite medical diagnosis had been made. Sugar had never been found in the urine on ordinary ward diet.

Time	Blood sugar per cent	Urine c. c. per hour	Urine sugar grams per hour
8.40	0.120	8.5	0
8.49	Glucose: 50 grams in 300 c. c. water.		
9.20	0.176	314	0
9.53	0.200	463	1.7
10.55	0.166	242	0.8
10.57	Glucose: 50 grams in 300 c. c. water.		
11.30	0.178	246	0.5
12.00	0.136	132	0.6
12.45	0.130	79	0

EXPERIMENT VI

J. H., male, black, married. Age: 39. Surgical No. 42151. Diagnosis: Exophthalmic goitre, adenoma of thyroid. No sugar had been found in the urine on the usual ward diet.

Time	Blood sugar per cent	Urine c. c. per hour	Urine sugar grams per hour
8.30	0.097	36	0
	Glucose: 100 grams in 300 c. c. water.		
9.00	0.130	64	0
9.30	0.196	31	0
10.05	0.177	73	0
10.45	0.161	49	0
	Glucose: 100 grams in 300 c. c. water.		
11.00	0.173	57	0
12.00	0.164	142	0
12.30	0.148	0	0
1.00	0.116	25	0

EXPERIMENT VII

Aurelius N., male, white, married. Age: 37. Medical No. 36828. Diagnosis: Bilateral facial palsy, psychoneurosis. No sugar appeared in the urine on the ordinary ward diet.

Time	Blood sugar per cent	Urine c. c. per hour	Urine sugar grams per hour
8.25	0.093	0	0
8.30	Glucose: 100 grams in 300 c. c. water.		
9.00	0.161	32	0
9.30	0.096	97	0
10.05	0.100	129	0
10.07	Glucose: 150 grams in 300 c. c. water.		
10.35	0.148	84	0
11.05	0.097	60	0
11.36	0.094	114	0

In the following patient the utilization of glucose is normal, although a small amount of sugar appears in the urine. The patient has a low renal threshold, that is, a mild grade of renal diabetes.

EXPERIMENT VIII

W. A. C., male, white, married. Age: 36. Diagnosis: Hyperthyroidism, psychoneurosis, renal diabetes. Small amount of sugar occasionally found in urine. A good deal of sugar in the urine after the ingestion of 75 grams of glucose.

Time	Blood sugar per cent	Urine c. c. per hour	Urine sugar grams per hour
8.30	0.088	43	0
8.40	Glucose: 100 grams in 300 c. c. water.		
9.10	0.125	92	Trace
9.35	Glucose: 100 grams in 300 c. c. water.		
9.43	0.105	251	0.2
10.10	0.085	658	0
10.50	0.084	216	0
11.40	0.084	68	0

It was found in testing several patients that they reacted to levulose in the same way that they did to glucose, only that the blood sugar rise was less marked. For instance, the diabetic whose response to glucose is detailed in experiment III gave the following response to levulose:

EXPERIMENT IX

A. B., (same patient as in Experiment III). Male, white, married. Age: 46. Dispensary No. 46750. A moderately severe diabetic who had become sugar-free on a carbohydrate diet.

Time	Blood sugar per cent	Urine c. c. per hour	Urine sugar grams per hour
8.30	0.167	66	0
8.34	Levulose: 20 grams in 300 c. c. water.		
9.01	0.177	36	0
9.33	0.194	68	0.5
10.32	0.177	150	0
11.00	0.177	329	0
11.02	Levulose: 20 grams in 300 c. c. water.		
11.35	0.167	178	0
12.10	0.184	103	0
1.00	0.184	144	0

CONCLUSIONS

1. The ingestion of glucose in some way stimulates the mechanism of carbohydrate disposal so that the repeated ingestion of the same amount causes a less marked hyperglycemia.
2. The same stimulating effect is noted in diabetes; the second dose is followed by a less marked hyperglycemia and glycosuria. However, the difference between the effects of the two doses is less marked than in normals and varies in different stages of the disease. Possibly, when the diabetes is very severe, the difference may completely vanish.
3. In renal glucosuria the normal stimulating effect of the ingestion of glucose is retained.
4. Levulose produces a much less marked hyperglycemia and glycosuria than does an equal amount of glucose.
5. The difference in the reaction of the normal and the diabetic is a quantitative not a qualitative difference.

REFERENCES

1. Hamman and Hirschman: *Archiv. Intern. Med.*, 1917, XX, 761.
2. Epstein: *Discussion: Soc. for Clinical Inves.*, May, 1916.
3. Woodyat: *Discussion: Assoc. American Phys.*, May, 1917.
4. Mosenthal and Hiller: *Jour. Biol. Chem.*, 1916, XXVIII, 197.
5. Joslin: *Treatment of diabetes mellitus*, 2d Edition, 1917.
6. Woodyat, Sansum and Wilder: *Jour. Am. Med. Assn.*, 1915, LXV, 2067.
7. Allen: *Glycosuria and diabetes*, 1913, Harvard Univ. Press.
8. Bang: *Der Blutzucker*, Wiesbaden, 1913.

BENZINE POISONING, WITH REPORT OF A CHRONIC CASE

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Benzine rarely causes poisoning, although it is largely used in the industrial world, especially for vulcanizing rubber, driving motors, cleaning, and as a drier in paints. Poisoning may be caused by either drinking or inhaling large amounts of the substance. The absorption of small quantities seldom produces ill effects.

Benzine is a product of petroleum. It is not to be confused with benzene or benzol which is obtained by the fractional distillation of coal tar. It is not a chemically pure body, but consists of that part of petroleum which distills over between 70° and 90° C. The mixture is made up of hydrocarbons of the general formula C_nH_{2n+2} , but consists principally of hexane, C_6H_{14} , and heptane, C_7H_{16} .

Numerous experiments have been made to determine the physiologic and toxic effects of benzine. Lehman¹ found that the inhalation of fumes by animals caused an irritation of the respiratory mucosa, muscular twitchings, and a slowly increasing narcosis. Felix² experimented on prisoners in Bucharest, administering benzine as one would chloroform for anesthesia. Small doses produced nausea, smarting of the conjunctivæ, and, in some cases, burning in the chest and drowsiness. Larger doses caused sleep and anesthesia, succeeded by nausea, vomiting, headache, dizziness, depression, and drowsiness. Montalti,³ after the internal administration of certain quantities, noted vomiting, uncomfortable feelings in the stomach, difficult breathing, miosis, muscle tremors, and symptoms of paralysis of the central nervous system. He concluded that gastrointestinal and cerebral toxic symptoms are characteristic for benzine intoxication. The action he thought to be due to the affinity of benzine for the fat, cholesterol, and lecithin group, which causes a change in the ganglion cells.

Hamilton⁴ interviewed nine interior house-painters who had experienced the effects of using a quick-drying paint containing large quantities of benzine in small and practically unventilated rooms. Dizziness, headache, spots before the eyes, dryness with choking in the throat, and burning of the eyelids were complained of by all, while some also had nausea, vomiting, pains in various parts of the abdomen, and dysuria. In several instances the worst discomfort developed on leaving work, the dizziness and staggering coming on in the open air.

A number of cases of acute poisoning are recorded in the literature; some in children who had drunk the benzine, while others had resulted from inhaling large amounts of the fumes, usually in cleaning tanks or vats in which there was very little ventilation. The symptoms noted as resulting from poisoning from drinking benzine have been cyanosis, miosis, weak pulse, unconsciousness, and convulsions. Friediger⁵ has collected 14 cases of poisoning by it, eight of which resulted in death. The fatal cases were all in children. Autopsy in all cases showed hemorrhages into the lungs.

The most prominent symptom in all cases of acute poisoning from the inhalation of fumes, according to Wichern,⁶ is the muscle tremor which may take the form of tonic or clonic cramps, the victims remaining almost without interruption in a condition of shaking fit. Wichern describes two cases: A workman was overcome by the fumes and fell into a tank of benzine. He was unconscious and showed wide, inactive pupils, spasticity, acrocyanosis, chills, and vomiting. In a second case, developing in a cleaning establishment, the symptoms were similar. Wichern states that in animal experiments muscle tremor is prominent also. Other observers have reported cases similar to those of Wichern. Peters⁷ describes the occurrence of retrobulbar neuritis in a girl of 14, the daughter of a glove-cleaner, who was addicted to the habit of inhaling benzine. The child was apathetic, stubborn, and learned slowly.

Chronic benzine poisoning seems to be of rare occurrence. According to Hamilton, ordinary workmen in American oil fields and refineries show no ill effects. Russian writers state that much ill health is caused by the constant inhalation of benzine fumes in establishments where the working conditions are bad. Only four cases of chronic poisoning are to be found in the literature, all occurring in a rubber factory, and two of which are reported in detail by Dorendorf.⁸ The first man after eight months in the factory began to have tearing pains in the muscles and joints of the extremities. Later he suffered from fibrillary twitching of the tongue and a fine tremor of the hands. After a rest he went back to work. Sixteen months later he returned to the hospital complaining of pressure in the head, weak memory, difficulty in speaking, anorexia, a feeling of heaviness in the limbs, and a feeling of cold in the right hand and leg. Examination showed psychic depression, hesitant speech, weakness of the right hand, hyperactive knee reflexes, and active tremor of the tongue, eyelids, and hand. The blood was normal except for the presence of free pigment. The second man was a worker in the vulcanizing room. A few weeks after beginning work he lost his appetite, he began to suffer from constipation, later from diarrhea, and finally from vomiting. He complained of headache and insomnia and had to stop work on account of colicky pains. He also had drawing pains in both arms and a sense of a leaden weight in the right arm with a feeling of coldness and formication. Examination showed the knee reflexes to be much increased and there was an after-tremor of the knee tendon. Striking the patella tendon evoked a contraction of the epigastric muscles and diaphragm. There was also tremor of the hands and tongue. Free pigment was found in the blood plasma, as in the first case. Dorendorf states that two other men were found in the same factory presenting similar symptoms. He allowed guinea-pigs to breathe the fumes of benzine

daily and found that they developed paresis and died in convulsions in 15 days.

The following case has been observed by us at The Johns Hopkins Hospital:

J. H. N., a white man, age 42, by occupation a cleaner in a lithographing factory, was admitted to the hospital October 4, 1915, complaining of weakness and dizziness.

Family History.—His father and four brothers died of pulmonary tuberculosis, but the patient has not been associated with his family for 25 years.

Previous Personal History.—The general health has been good up to two years ago. He had pneumonia at 28 and malaria twice yearly for 10 years. He has not had an attack of malaria for the past eight years. During the past four years he has had at times severe night sweats with cough lasting for three to four weeks. The last attack occurred two weeks before admission. He has never been jaundiced until his present illness. He had dysentery with blood and mucus in the stools in Cuba in 1897. Three years ago his appendix was removed and his right kidney suspended. For 11 years previous to this operation he had had attacks of abdominal pain with a sensation of a sliding mass in the abdomen.

Present Illness.—The patient states that he has not been strong since the operation, but in July, 1914, he felt fairly well except for some weakness. Two months after beginning his present work he began to have generalized pains over his abdomen with nausea and vomiting after meals. He also had a feeling in his head which he describes as a "compression on the inside" or a "pressing-in like." On October 1, 1914, he went to a hospital. At this time he also had a feeling of heaviness in the arms and legs, which made them feel like leaden weights. These symptoms cleared up, but on going back to work the nausea, vomiting, and dizziness returned and have become progressively worse. The nausea and dizziness have often been so severe that he has had to leave work. He has been gradually losing strength, the weakness before admission being so extreme that it often took an hour to walk to his home when it had ordinarily required only 12 minutes. At times he has fallen in the street. For the past three months he has been getting drowsy, his memory has been failing, and he has had difficulty in thinking. He has had a feeling of coldness in his legs for the past two months, which he describes as a feeling "as if menthol were rubbed on them." He has had shooting pains in the arms with cramp in the muscles ending in hyperextension of the fingers. Recently he has had spontaneous cramps of other muscles. His legs felt as if "a thousand needles were stuck in them." The sense of heaviness of the limbs continued until they felt like "bags of cement." He has noticed, also, tremor of the fingers and eyelids and failing memory; his head has not felt clear, and the left ear feels as if bubbles were flowing out of it. During all this time the nausea, vomiting, dizziness, and weakness have been progressive. He has had some dimness of vision. Five weeks before entering the hospital he noticed that his urine was becoming dark. Two days ago someone told him that he was jaundiced. He has had marked anorexia and constipation.

Physical Examination.—The patient is undernourished and looks sick. He is very dull mentally, and answers questions slowly. He does not seem able to think clearly. The lips are cyanosed. There is well-marked jaundice of the skin and mucous membranes. There is a sweetish odor to the breath. The pupils are equal and active. There is no glandular enlargement. There are signs of fibroid changes at both apices. The heart is negative. Blood pressure 100/65. The liver edge extends two finger-breadths below the costal margin and is firm and tender. The

spleen is palpable. The tendon reflexes are very active everywhere, but equal on the two sides. When the patella tendon on one side is struck there is a contraction of the thigh muscles on the opposite side. The superficial reflexes are present. Babinski and Oppenheim negative. There is no clonus; sensory examination is negative.

Laboratory Examination.—Wassermann (blood) negative. Sputum negative for tubercle bacilli. The urine had a specific gravity of 1022 and was negative throughout except for an occasional trace of albumin and a positive bile test on admission. Blood (October 6): R. B. C., 4,332,000; W. B. C., 4550; Hb., 77 per cent; differential: P. M. N., 54.6 per cent; P. M. E., 2.6 per cent; S. M., 33.3 per cent; L. M., 5.0 per cent; trans., 3.0 per cent; unclassified, 1.3 per cent. Gastric analysis: Free HCL, 44 per cent, and total acidity, 72 per cent. The stool was dark brown and gave a positive bile test. There were no parasites or ova. On October 8 the white blood cells were 5400. A Calmette tuberculin test was negative with 1 per cent and 5 per cent. Four other blood counts showed the white blood cells to be below 5000. A second test meal was given with the same findings as in the first. On November 23 the white cells had risen to 7280.

Course in Hospital.—The symptoms rapidly disappeared. The reflexes continued active for a long while. At times striking the patella tendon would cause a contraction of nearly all the larger muscle groups. The jaundice and cyanosis cleared up. He gained weight rapidly and no longer had difficulty in thinking. He was discharged from the hospital November 23, 1915. At this time the reflexes were moderately exaggerated. Examination otherwise was negative. When seen several months later there had been no return of the symptoms.

The factory at which the patient worked was visited. It was found that the lithographing rolls were dropped into a trough, six feet long and one foot wide, filled with benzine, and scrubbed clean. About two gallons of benzine evaporated from the trough daily. The room in which the work was done was large, but from the nature of the lithographing inks it had to be tightly closed to prevent the ink from drying. The patient had worked for over a year five hours daily at this trough where he was continually inhaling the fumes. No other workmen showed signs of benzine intoxication, but there were no others engaged in the same kind of work.

Formerly each printer had been required to clean the rolls from his machine, and this took only a few minutes each day. The patient had been cleaning all the rolls for the entire factory.

SUMMARY

Chronic benzine poisoning is uncommon, but may occur. The symptoms complained of are referable almost entirely to the gastrointestinal tract and the central nervous system.

REFERENCES.

1. Quoted by Hamilton.
2. Quoted by Zornlaib: Wien. Med. Wchnschr., 1906, LVI, 366.
3. Hamilton: Kober and Hanson, Diseases of Occupation and Vocational Hygiene, Phil., 1916.
4. Friediger: Münch. Med. Wchnschr., 1912, LIX, 252.
5. Wichern: Münch. Med. Wchnschr., 1909, LVI, 2.
6. Peters: Deut. Med. Wchnschr., 1900, XXVI, 249.
7. Dorendorf: Münch. Med. Wchnschr., 1901, XLVIII, 236.

THE REACTION OF MONKEYS TO THE INOCULATION OF MEASLES BLOOD

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In attempting the transmission of an infectious disease from man to lower animals it is not to be expected, in the case of a refractory species, that the typical clinical symptoms will be reproduced exactly. A distinct advance has been accomplished if one can obtain regularly even a single characteristic feature of the disease; a definite reaction occurring with reasonable constancy as the result of inoculation of the virus would enable one to determine many of the essential characteristics of the disease in question. Such reactions have been described as the result of the inoculation of monkeys with the blood of measles patients; one may mention more especially reports of the occurrence of rashes, of leucopenia and of Koplik spots. Wentworth and myself attempted to confirm this work.¹ The results of the intensive inoculation of a small group of monkeys were very discouraging and led to the conclusion that the reactions were too indefinite and inconstant to permit the practical use of monkeys in testing the blood of patients for the virus of measles. The present note will record some further observations on the question whether the occasional slight and indefinite symptoms observed in monkeys represent a reaction to the virus of measles. It is of theoretical interest to determine whether the virus of the disease can at times multiply and produce minor symptoms in an occasional individual animal.

Summary of Literature. Josias² in 1898 reported the successful transmission of measles to three monkeys ("Sajous capucin" and "Sajous robustus"). These animals were inoculated on the mucous membrane with the mucous secretions from cases in full eruption and one monkey received in addition an injection of blood. The incubation periods were 27 days, 13 days and 11 days, respectively. In these three animals; the rash was not remarkable, and the rise in temperature was not striking. Anderson and Goldberger³ were the first investigators to report the infection of monkeys with measles by the injection of blood alone. Successful results were obtained in all species tested, namely, *Macacus rhesus*, *cynomolgus* and *sinicus*. The work was carried out on an extensive scale. The symptoms observed most commonly consisted of coryza and rhinitis, slight rash, malaise and occasionally some febrile disturbances. The rash was sometimes pink, sometimes copper-colored; it appeared, as a rule, 10 days after injection though the extreme limits varied widely, being from seven days to 21 and possibly 26 days. The febrile disturbance, in those experiments in which the temperature reaction was described in detail, was extremely slight, being insufficient of itself to permit a diagnosis. Moreover, it is noteworthy that sometimes the febrile period and the eruptive period did not coincide. In working with secretions from the mucous membranes these authors produced symptoms by subcutaneous injection of the secretions, but not by inoculation on the mucous membranes of monkeys.

Hektoen and Eggers⁴ inoculated three monkeys with blood from measles patients. Each of these animals developed more or less leucopenia though, as emphasized by these authors, the leucocyte count in normal monkeys fluctuates rather widely and without any apparent cause. Two of the three animals remained free from any rash; the other developed a faint eruption about the eyes and the groin 15 days after injection. No Koplik spots were found.

Subinoculations were made from monkey to monkey in three instances under conditions which were not especially favorable; the results were not striking.

Lucas and Prizer⁵ injected two monkeys with blood from a pre-eruptive case of measles. They noted a subsequent leucopenia, and the development of Koplik spots ten days after injection. On subinoculation of two other monkeys, one also developed Koplik spots ten days after injection. No definite rashes developed, but these animals showed a transient erythema limited to the face. In one animal an erythema and a conjunctivitis were noted as occurring three days after the appearance of Koplik spots and one day after the administration of ether. No febrile reactions developed in any of these animals.

Tunncliffe⁶ reported the development of a leucopenia in a monkey injected with measles blood, whereas a control monkey maintained a normal white count after the injection of normal blood. No mention is made of the occurrence of any rash or other symptoms of measles.

Nicolle and Conseil⁷ injected one monkey (*M. sinicus*) with measles blood withdrawn 24 hours before the appearance of the eruption. A rise in temperature occurred, but no mention is made of any rash.

Jurgelunas⁸ inoculated monkeys with blood of measles patients, with secretions from the mucous membranes and exposed some animals in a measles ward. The results were essentially negative. Especial attention was given to the nasal secretions; of the animals inoculated with blood, one died 11 days after injection from an undetermined cause; another received only a subcutaneous injection; for a third, the blood for injection was not taken until the second day of the patient's rash.

From this summary it is seen that there are definite reports of the successful transmission of measles to monkeys. Attempts to infect other animals have been uniformly disappointing. According to the literature, all of the important features of measles have been reproduced in monkeys, namely, the rash, Koplik spots, leucopenia, respiratory symptoms, fever and malaise. It is rather striking, however, that no single investigator has ever obtained all of these features in any single individual or even in a series of animals. Moreover, there is no single symptom which appears at all constantly. The periods of incubation vary widely. Even under favorable conditions a large proportion of animals remain entirely normal.

EXPERIMENTAL WORK

In the course of some investigations involving the inoculation of human volunteers, advantage was taken of the opportunity to conduct simultaneous injections of monkeys, thereby permitting a comparison of the results obtained in a refractory and in a highly susceptible species.

Injection of Blood.—Specimens of blood were collected in an approximately equal volume of citrate solution from two cases of measles in the pre-eruptive stage. The two specimens of citrated blood were mixed and injected as follows: 4 c. c. were injected into each of two adult monkeys (*Macacus rhesus*), half being given subcutaneously and the rest intramuscularly; 6 c. c. of the mixed specimens were injected into

each of two susceptible human volunteers, part of the material being given subcutaneously and the remainder intramuscularly. On the next day, blood was again taken from each of the measles patients; one had developed a rash 18 hours previously and the other was free from any eruption, the rash appearing six hours later. The specimens of blood were mixed and injected as on the preceding days into the two animals and also into the volunteers.* The relative dosage and the mode of injection for the monkeys, therefore, differed from that employed in the volunteers; it seemed desirable for the inoculations of the monkeys to adhere to conditions which would give the maximal opportunity for producing an infection.

These monkeys were examined for any evidences of respiratory symptoms, of malaise, of an exanthem and also Koplik spots. The temperatures (rectal) were taken twice daily, at about 9 o'clock in the morning and at 4 o'clock in the afternoon, before the feeding periods. The white counts were made, as a routine, in the morning only. Neither animal developed any significant rise in temperature. Rhesus I showed a low leucocyte count which persisted for only two days and did not appear until the 11th day after injection. Rhesus II developed a leucopenia which began on the sixth day after injection and persisted for three or four days. The counts in this animal subsequently became complicated by the development of a severe pneumonia. The records are as follows:

INOCULATIONS OF MONKEYS WITH MEASLES BLOOD

Days after first inoculation	Rhesus I			Rhesus II			Additional observations on Rhesus II
	Temp.		White count	Temp.		White count	
	A. M.	P. M.		A. M.	P. M.		
1	101.2	18,900	101.8	13,900	
2	99.0	102.0	11,100	100.4	102.2	10,700	
3	99.4	101.8	10,100	101.8	101.0	18,500	
4	101.0	102.4	11,800	102.0	102.0	10,000	
5	101.2	102.0	12,500	100.6	102.0	11,800	
6	100.8	102.2	14,900	102.2	102.8	5,500	At noon, temperature 102.4.
7	101.6	101.8	8,300	102.4	102.0	6,200	Count, 6,300.
8	100.8	101.2	9,500	101.2	101.8	5,600	Bled for inoculation of volunteer.
9	100.8	102.4	4,700	101.6	102.0	7,900	At noon, temperature 102.0.
10	101.6	7,400 ¹	101.2	9,900	Count 7,700.
11	101.4	101.8	4,400	102.8	103.6	11,110	Room temperature, forenoon
12	101.2	102.6	5,700	101.0	101.4	12,600	65°, in afternoon 80°.
13	101.6	102.9	4,600 ¹	101.0	102.0	8,200	Slight rash.
14	100.9	102.2	9,200	100.0	101.0	6,400	
15	101.4	102.0	8,900	100.0	100.0	6,000	Early signs of pneumonia.
16	100.6	101.0	8,300	99.4	99.8	6,600	Definite pneumonia.
17	100.6	102.2	17,300	98.8	100.6	18,400	Critically ill.
18	102.0	102.2	13,900	101.0	9,400	Critically ill.
20	101.2	14,500	100.8	44,000	Marked improvement by crisis.

¹ White counts in afternoon.² At noon, temperature 101.0, count 15,400.³ At noon, temperature 101.2, count 5,600.

* The precautions observed in the protection and selection of the volunteers (VIII and IX), as well as the details concerning their inoculation, are given in the September number of this BULLETIN.

Rhesus I developed no respiratory or constitutional symptoms and no evidence of an exanthem or of Koplik spots. Rhesus II was bled on the second day of his leucopenia and at the beginning of the seventh day after the first of his two inoculations. Three c. c. of blood were mixed with 2 c. c. of 2.5 per cent sodium citrate in physiological saline and injected intramuscularly and subcutaneously in the gluteal region into a susceptible human volunteer. No local or general symptoms developed; the temperature and white count remained normal.

Rhesus II at the beginning of the 12th day after the first injection developed a faint but distinct rash over the face and uppermost part of the thorax. In some areas, especially over the chest, a diffuse erythematous blush was present. Around the eyes and nose there occurred discrete macules from 1 to 2 mm. in diameter; these were especially marked around the hair follicles. Moderate but definite malaise was present on this day only. On the second day the rash faded almost completely, leaving behind only very slightly pigmented areas; by the third day this pigmentation had disappeared. On the next day an outspoken and very severe pneumonia developed, probably as the result of the deep and prolonged etherization employed during the collection of blood in the previous week. A blood culture, taken after the pneumonia was fully developed, showed no growth.

The rash developing in this animal after an incubation period corresponding to that in human cases was in no way characteristic of the exanthem as it occurs in man. However, it is not to be expected that the skin eruptions developing in a lower animal would necessarily conform to the human exanthem. This consideration greatly increases the difficulty of determining whether an atypical rash is due to the virus of measles. The principal points bearing on the interpretation of this exanthem are:

1. The period of incubation.
2. The results of the inoculation of blood from the monkey into a susceptible individual.
3. The behavior of susceptible human volunteers inoculated with the same specimen of blood which was injected into the monkeys.
4. The exclusion of other factors.

The period of incubation in this animal, 12 days, would conform very well with the diagnosis of measles.

The negative result of the inoculation of blood from the monkey into man might be explained on two grounds; either the supposedly susceptible volunteer may in reality have been immune or the single specimen of monkey's blood may not have been taken at the most favorable period for transmitting the disease.

The absence of any symptoms in the two volunteers inoculated from the same specimen of blood that was used for the monkeys does not constitute final proof, but it speaks very strongly against ascribing this rash to the virus of measles. It does not seem plausible that a highly refractory animal would be overwhelmed by a large inoculation intraperitoneally, if an extremely susceptible host escapes infection after a moderately large subcutaneous and intramuscular injection.

Of other factors which might give rise to a rash under the conditions of the experiment the question of serum sickness requires consideration. This possibility is important, even though anaphylaxis has not been described in monkeys; and serum rashes, which are presumably a manifestation of anaphylaxis, have not been produced in lower animals. The two conditions, measles and serum sickness, have certain features in common. In either condition, the constitutional symptoms may be very mild. The incubation periods are almost identical, the 12th day being known as the critical day in serum disease. The rash of serum disease is altogether protean in character; the exanthem under discussion resembled serum rashes more closely than the eruption of measles.

The eruption in monkeys does not occur constantly after the injection of measles blood. Indeed, the indefinite character of the rash and its comparatively low incidence considerably increases the difficulty of determining its cause. There are certain points which would favor the view that the rashes observed by Anderson and Goldberger were not due to serum disease. These authors report that several monkeys developed no rash when injected with moderately large amounts of human blood from advanced cases of measles which presumably did not contain the virus of the disease. Moreover, in performing subinoculations, a rash sometimes developed when monkeys were injected with the blood of other monkeys; from their description it would seem that these rashes were less striking than those obtained with measles blood from human cases. Anderson and Goldberger also observed rashes after the inoculation of nasal secretions, thereby affording conditions in which anaphylactic manifestations would not occur. These rashes developed only in animals injected subcutaneously with secretions; two monkeys inoculated on the mucous membranes developed no symptoms. The possibility of producing bacterial septicæmia by these injections must be borne in mind; in one instance it was noted that, at the time a rash appeared, blood cultures showed the presence of a micrococcus.

It seemed desirable to test the possibility of producing a serum rash in monkeys. Human serum was employed for one group of animals and, in order to obtain more favorable conditions for the production of anaphylaxis, another set was injected with normal horse serum. Ten animals in all were inoculated. Eight of these (*Macacus syriacus*) had received no previous treatment with serum; the two (*M. rhesus*) which were injected with measles blood were reinjected with normal serum. All of the animals were injected intravenously and the majority also received intraperitoneal or subcutaneous injections either at the time of the intravenous injection or after an interval of one or two days. Assuming that serum sickness represents a reaction between antigen and antibody it was considered that the injection of large amounts of serum by different routes would afford a maximal opportunity for the coexistence of antigen and antibody within the organism.

Observations were continued over a period of three weeks. Of these ten animals six remained entirely negative and four

developed a very faint erythematous blush eight to ten days after injection. This appeared on the face and uppermost part of the chest, persisting for two or three days. It disappeared on pressure and was not followed by pigmentation or desquamation. Some of these animals showed slight loss of appetite at this time, but there was no definite evidence of malaise. The erythema in Rhesus II appeared 10 days after the second injection and persisted for three days. The symptoms were less definite than after his first injection with measles blood. These two rhesus monkeys were of the same size and apparently the same age; one reacted slightly both to the injections of measles blood and normal blood, while the other reacted to neither. The second injection of human serum in these animals produced no clinical symptoms of anaphylactic shock.

The following table gives the details of these injections:

INJECTIONS OF MONKEYS WITH SERUM

Serial number	Species of monkey	Material injected	Amount injected			Result
			Subcutaneously	Intraperitoneally	Intravenously	
1	<i>M. rhesus</i>	Measles blood	1 c.c.	c.c.	None	No effect.
10 weeks later		Human serum	None	None	5 c.c.	No effect.
2	<i>M. rhesus</i>	Measles blood	1 c.c.	1 c.c.	None	Definite rash.
10 weeks later		Human serum	None	None	5 c.c.	
3 days later		Human serum	None	10 c.c.	None	Slight erythema 10 days later.
3	<i>M. syriacus</i>	Human serum	3 c.c.	None	7 c.c.	
2 days later		Human serum	None	1 c.c.	None	Slight erythema 8 days later.
4	<i>M. syriacus</i>	Human serum	2 c.c.	5 c.c.	3 c.c.	
2 days later		Human serum	None	10 c.c.	None	No effect.
5	<i>M. syriacus</i>	Horse serum	None	None	5 c.c.	No effect.
6	<i>M. syriacus</i>	Horse serum	1 c.c.	None	5 c.c.	
1 day later		Horse serum	None	10 c.c.	None	Slight erythema 8 days later.
7	<i>M. syriacus</i>	Horse serum	None	None	5 c.c.	
1 day later		Horse serum	None	10 c.c.	None	Slight erythema 9 days later.
8	<i>M. syriacus</i>	Horse serum	None	5 c.c.	5 c.c.	
1 day later		Horse serum	None	10 c.c.	None	No effect.
9	<i>M. syriacus</i>	Horse serum	3 c.c.	None	7 c.c.	No effect.
10	<i>M. syriacus</i>	Horse serum	None	None	5 c.c.	
1 day later		Horse serum	None	10 c.c.	None	No effect.

The slight erythema produced in some of these animals was by no means sufficient to permit of its interpretation as a serum rash; the symptoms, however, did appear to correspond fairly well with some of the indefinite rashes to which some authors attach significance in the diagnosis of measles. A very slight reaction is sufficient to complicate the interpretation of the delicate and inconstant effect resulting from the injection of measles blood.

SUMMARY

1. Blood from two early cases of measles in the pre-eruptive and later in the early eruptive stage was injected subcutaneously and intraperitoneally into two monkeys. One

animal remained free from symptoms; the other developed a moderate leucopœnia and later a slight rash.

2. A portion of the same specimen of measles blood was injected subcutaneously and intramuscularly into two susceptible human volunteers. No symptoms resulted.

3. A specimen of blood from the monkey which subsequently developed a rash was injected into a susceptible volunteer, but produced no symptoms.

4. Normal serum injected into monkeys was followed by a very slight erythema appearing about eight to ten days after injection in four of ten animals.

5. The weight of evidence in these experiments is against the interpretation of the symptoms in this monkey as representing a reaction to the virus of measles.

LITERATURE

1. Sellards, A. W., and Wentworth, J. A.: *Bull. Johns Hopkins Hosp.*, 1919, XXX, 57.
2. Josias, A.: *Tribune méd.*, 1898, XXIX, 211.
3. Anderson, J. F., and Goldberger, J.: *Pub. Health Rep.*, 1911, XXVI, 847, 887; *Jour. Amer. Med. Assn.*, 1911, LVII, 113, 476, 971, 1612.
4. Hektoen, L., and Eggers, H. E.: *Jour. Amer. Med. Assn.*, 1911, LVII, 1833.
5. Lucas, W. P., and Prizer, E. L.: *Jour. Med. Research*, 1912, XXVI, 181.
6. Tunncliffe, R.: *Jour. Infect. Dis.*, 1912, XI, 474.
7. Nicolle, C., and Conseil, E.: *Compt. rend. acad. scien.*, 1911, CLIII, 1522.
8. Jurgelunas, A.: *Centralbl. f. Bakteriöl., Orig.*, 1914, LXXII, 483.

NOTES ON NEW BOOKS

The Nervous Heart. By R. M. WILSON and J. H. CARROLL. (London: Henry Froude; Hodder and Stoughton, 1919.)

The book represents an attempt to explain "Disordered Action of the Heart" (D. A. H.), as well as post-febrile "functional heart disorders" by disturbances of the nervous control of the heart. The basic theories need more proof before the deductions can be accepted. Nothing new is added to the prognosis or treatment of the functional heart disorders described.

V. R. M.

Burns and Their Treatment. By J. M. H. MACLEOD. Cloth, \$2.00. (London: Henry Froude; Hodder and Stoughton, 1918.)

The subject of burns and especially their treatment is always of vital significance; and although the author has added nothing really new or radical to our general knowledge of the subject, he has given us a brief and excellent epitome of the modern conception of burns. Better still, the fact that he has recorded his personal experiences based on contact with a vast amount of material adds additional interest.

In the eleven chapters the different aspects of the subject are taken up as follows: Burns from Heat (five chapters), Electricity, Lightning, X-Rays and Radium, Solar Burns, Corrosives, High Explosives.

The fact that the author is a dermatologist of note makes his descriptive and pathological comments especially valuable. It is regrettable that compactness has allowed a place for so few illustrations. Despite its small size, however, the book, which is intended apparently to fit the coat-pocket, contains a great store of information.

The subject matter is attractively presented. The book has been carefully edited and is well printed. It should certainly serve the purpose of assisting the reader in keeping abreast of modern advances in this interesting subject.

I. R. P.

A Study of the Mental Life of the Child. By DR. H. VON HUG-HELLMUTH. Paper, \$2.00. (Washington: Nervous and Mental Disease Publishing Company, 1919.)

The author divides her study into two periods, the period of infancy and the period of play. Thirty-nine pages are devoted to the former, the rest of the book to the latter. It is not possible to summarize the detailed observations which are found throughout the book, or to refer to the author's interpretations of many

of the phenomena of childhood, but the chief value of the book lies in these detailed observations, and in the endeavor to interpret them in terms of the actual driving forces of human life.

In discussing the child as he actually is, there is no topic censored, and thus in a way we have the most honest book on child psychology available. The author, however, goes even further than showing lack of embarrassment in dealing with the sexual life of the child, with its interest in matters of the toilet and so on; she exhibits the Freudian tendency to identify pleasure with sexual pleasure, and thus a sexual interpretation of very doubtful validity is given to many phenomena. She comes to her topic steeped in the Freudian dogmas, sharing the tendency of the Freudian School to generalize, to push hypothesis to an extreme, and to equate hypothesis with actual observation of fact.

Notwithstanding this extreme attitude, which to some extent distorts its proportions, the book is one that deserves the serious study of any one interested in the psychology of childhood.

C. McF. C.

Physiology and Biochemistry in Modern Medicine. By J. J. R. MACLEOD. (St. Louis: C. V. Mosby Company, 1918.)

This book is intended by the author to be "an advanced text in physiology for those about to enter upon their clinical instruction and, at the same time, a review for those of a maturer clinical experience who may desire to seek the physiological interpretation of diseased conditions." It is published in an attractive form and contains many good illustrations. The treatment of the subject matter is, in general, clear, and would appear to be well done for the reader for whom it is intended. Of particular present day interest from the point of view of the clinician are those sections dealing with the respiration, the circulation, and the excretion of urine. The book is a most praiseworthy production, and deserves a wide reading among those who have at heart the closer union of physiology and the allied sciences with clinical medicine.

H.

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- Royal College of Physicians of London.* Catalogue of the Library. 1912. 8°. 1354 pages. Spottiswoode & Co., Ltd., London.
- Colloids in Biology and Medicine.* By Prof. H. Bechhold. Authorized Translation from the Second German Edition, With Notes and Emendations. By Jesse G. M. Bullowa, A. B., M. D. 54 illustrations. 1919. 8°. 464 pages. D. Van Nostrand Company, New York.
- Diseases of the Skin.* By James H. Sequeira. Third edition, with 52 plates in color and 257 text-figures. 1919. 8°. 644 pages. P. Blakiston's Son & Co., Philadelphia.
- Medical Society of London.* Transactions of the Medical Society of London. Volume the forty-first. Edited by Hugh Lett, F. R. C. S. and Edmund Cautley, M. D. 1918. 8°. 302 pages. Printed for the Society, by Harrison & Sons, London.
- University of Iowa Studies in Medicine.* First Series No. 24. Collected Studies and Reports. Volume I, Number 5, January, 1919. 8°. Published by University, Iowa City.
- Monographs of the Rockefeller Institute for Medical Research.* No. 10, April 16, 1919. *The Pathology of the Pneumonia in the United States Army Camps During the Winter of 1917-18.* By William G. MacCallum, M. D. 1919. 8°. 147 pages. The Rockefeller Institute for Medical Research, New York.
- Transactions of the Section on Genito-Urinary Diseases of the American Medical Association.* At the Sixty-ninth Annual Session, Held at Chicago, June 10 to 14, 1918. 8°. 302 pages. American Medical Association Press, Chicago.
- American Surgical Association.* Transactions of the American Surgical Association. Volume the thirty-sixth. Edited by John F. Binnie, M. D. 1918. 8°. 602 pages. Printed for the Association, Philadelphia.
- George Williams Hooper Foundation for Medical Research.* The Department of Research Medicine of the University of California Medical School, San Francisco. Collected Reprints. Volume III, 1917-1918. San Francisco, California.
- Colloid Chemistry, An Introduction, With Some Practical Applications.* By Jerome Alexander, M. Sc. Illustrated. 1919. 16°. 90 pages. D. Van Nostrand Company, New York.
- The Blind.* Their Condition and the Work Being Done for Them in the United States. By Harry Best, Ph. D. 1919. 8°. 763 pages. Macmillan Company, New York.
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- The Soldier's Heart and the Effort Syndrome.* By Thomas Lewis, M. D., F. R. C. P., F. R. S., D. Sc. 1918. 8°. 144 pages. Shaw & Sons, London; Paul B. Hoeber, New York.
- The Internal Secretions and the Nervous System.* By Dr. M. Laignel-Lavastine. Authorized Translation by Dr. F. T. Robeson. Nervous and Mental Disease Monograph Series No. 30. 1919. 8°. 59 pages. Nervous and Mental Disease Publishing Company, New York and Washington.
- Aspects of Death and Correlated Aspects of Life in Art, Epigram, and Poetry.* Contributions Towards an Anthology and an Iconography of the Subject. Illustrated Especially by Medals, Engraved Gems, Jewels, Ivories, Antique Pottery, etc. By Frederick Parkes Weber, M. A., M. D., F. R. C. P., F. S. A. Third edition, revised and much enlarged. With 145 illustrations. 1918. 8°. 786 pages. Paul B. Hoeber, New York.
- Association of American Physicians.* Transactions of the Association of American Physicians. Thirty-third Session Held at Atlantic City, N. J., May 7 and 8, 1918. Volume XXXIII. 1918. 8°. 427 pages. Printed for the Association. Philadelphia.
- National Tuberculosis Association.* Transactions of the Fourteenth Annual Meeting, Boston, Mass., June 6-8, 1918. 8°. 608 pages. National Tuberculosis Association, New York.
- The Smithsonian Institution.* Annual Report of the Board of Regents of the Smithsonian Institution. Showing the Operations, Expenditures, and Condition of the Institution for the Year Ending June 30, 1916. 1917. 8°. 607 pages. Government Printing Office, Washington.
- Geriatrics.* A Treatise on Senile Conditions, Diseases of Advanced Life, and Care of the Aged. By Malford W. Thewlis, M. D. With introduction by A. Jacobi, M. D., LL. D., and I. L. Nascher, M. D. 1919. 8°. 250 pages. C. V. Mosby Company, St. Louis.
- American College of Surgeons.* Sixth Year Book 1918-1919. 8°. 543 pages. Chicago.
- Mortality Statistics of Insured Wage-Earners and Their Families.* Experience of the Metropolitan Life Insurance Company Industrial Department, 1911 to 1916, in the United States and Canada. By Louis I. Dublin, Ph. D. With the collaboration of Edwin W. Kopf and George H. Van Buren. 1919. 8°. 397 pages. Metropolitan Life Insurance Company, New York.
- The Peritoncum.* Volume I. Structure and Function in Relation to the Principles of Abdominal Surgery. Volume II. Diseases and Their Treatment. By Arthur E. Hertzler, M. D., F. A. C. S. 1919. 8°. 870 pages. C. V. Mosby Company, St. Louis.
- A Manual of Exercises for the Correction of Speech Disorders.* By May Kirk Scripture, B. A., and Eugene Jackson, B. A. Illustrated. 1919. 12°. 236 pages. F. A. Davis Company, Philadelphia.
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- The Erotic Motive in Literature.* By Albert Mordell. 1919. 12°. 250 pages. Boni and Liveright, New York.
- Symptoms of Visceral Disease.* A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine. By Francis Marion Pottenger, A. M., LL. D., F. A. C. P. With 86 text illustrations and nine color plates. 1919. 8°. 328 pages. C. V. Mosby Company, St. Louis.
- Gynoplastic Technology.* With a chapter on "Sacral Anesthesia." By Arnold Sturmdorf, M. D. Illustrated with 152 half-tone and photo-engravings in the text, some in colors, and 23 full-page plates, with 35 figures, all in colors. 1919. 8°. 334 pages. F. A. Davis Company, Philadelphia; Stanley Phillips, London.
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THE FATE OF BACTERIA INTRODUCED INTO THE UPPER AIR PASSAGES

By ARTHUR L. BLOOMFIELD

(From the Medical Clinic, The Johns Hopkins University and Hospital.)

In considering the pathogenesis of infectious diseases in which the portal of entry is in the upper respiratory tract, three factors must be reckoned with: first, the means whereby the virus is conveyed to the individual; secondly, the fate of the organism from the time it reaches the mouth or nose until it is eliminated or until invasion takes place; and third, the actual invasion of the virus into the body. Although many details of the mode of conveyance of bacteria from one host to another have been adequately determined, we possess little exact information about the localization, growth and disposal of such organisms, and the factors which determine a longer or shorter period of survival in the upper air passages before or after invasion has taken place. Studies of contact infection and of carrier incidence and persistence under various conditions afford indirect information, which is, however, inadequate to solve the detailed problems of particular infections. By actually introducing bacteria into the upper air passages in such a way that the dose, exact time and site of inoculation, and other conditions can be controlled, and by studying the fate of such organisms, it seems probable that knowledge of the details of the spread of bacteria and of the development of the carrier state can be extended.

It seemed advisable to make a preliminary study of the fate of non-pathogenic organisms before employing possible disease producers. To be satisfactory for this purpose, an organism was sought which was non-pathogenic, not normally present in the upper air passages of man, which could be readily grown on simple media, which could be easily recognized both in culture and in smear, and which would not be overgrown in culture by the normal mouth flora. After examining a number of strains, a *sarcina lutea* was selected as fulfilling these criteria. The organism employed* had the following characteristics:

Morphology.—Rather small *sarcinae*, varying in size, occurring for the most part in regular packets, singly or in pairs, but sometimes in irregular groups. They measure 0.66 to 1.13 microns in 20-hour cultures on plain agar.

Motility.—Non motile.

Staining Properties.—Gram positive.

Cultural Characteristics.—Agar slant. Growth lemon yellow, at first translucent and rather dull, later, opaque and bright in color, rather thick, raised.

Agar Colonies.—Round with smooth edges, lemon yellow, opaque; surface smooth and glistening. Under low power—margin smooth, sharply defined, surface finely granular, color yellowish grey.

* The culture was kindly supplied by Dr. W. W. Ford.

Broth.—Liquid clouded at first with small amount of viscid sediment; later, liquid clear, with large amount of sediment, very viscid and stringy, yellow, no pellicle.

Peptone Solution.—Less growth than in broth.

Litmus milk.—Unchanged.

Pigment formation often not marked until after the lapse of 48 hours; on very acid or alkaline media, or when grown with certain other organisms, pigment formation may be very slight, but there is always a definite yellowish tint.

The organism grows well in mixed culture with the bacteria usually present in the mouth, and it does not tend to be overgrown except in occasional instances in which a "spreader" rapidly covers the entire plate. The colonies of *sarcina lutea* grow well side by side with, and at times partly superimposed on, those of the mouth bacteria.

This organism was not found in the air passages of any of the controls; and it is entirely non-pathogenic for human beings.

METHODS

Individuals were selected whose mouths and upper air passages presented no acute disease or abnormality other than those usually encountered, such as pyorrhea, dental caries, adherent tonsils, and minor grades of septal or turbinate deformity. From the point of view of this experiment, they could be regarded as normal. The patients were kept under direct observation during the first hour of the experiment and for the most part took nothing by mouth during this time. The inoculations were always made several hours after eating, when the mouth was free from gross food particles.

Solid masses of a 24-hour growth of *sarcina lutea* on plain agar were swabbed on the selected site, and cultures taken at regular intervals thereafter. They were made for the most part by scraping the mucous membrane with a heavy platinum loop, 0.5 cm. in diameter, and rubbing up the mucus obtained in this way in a drop of sterile salt solution. This was spread over several agar plates in varying dilutions. It was found that many more organisms were recovered by this method than by the usual swab technique. There was usually a uniform discrete spread of colonies. This point is emphasized because we feel that overgrowth in the plates was eliminated and that we obtained a true representation of the percentage of viable organisms present in the swab. The plates were kept for at least a week and the organisms identified by the appearance of colonies and by smears.

Experiment I.—*Sarcina lutea* was swabbed on the tongue and cultures were made immediately, and at 10-minute, 1-hour, 24-hour and 48-hour intervals. The results are summarized in Table I.

Summary.—*Sarcina lutea* swabbed on the tongue disappeared very rapidly. Only a few colonies could be recovered from the site of inoculation after ten minutes, and practically none at the end of one hour. Simultaneous cultures from the pharynx, except in one instance, yielded only a few colonies during the first ten minutes.

Experiment II.—*Sarcina lutea* was swabbed on the nasal mucosa and cultures made immediately and at 10-minute, 1-hour, 24-hour and 48-hour intervals. The results are summarized in Table II.

Summary.—*Sarcina lutea* swabbed on the nasal mucosa persisted longer than on the tongue, but in only one of five cases could a few colonies (7) be recovered after 24 hours. In spite of the heavy inoculation, only a few colonies could be obtained in nasopharynx cultures made simultaneously with the nose cultures.

Experiment III.—*Sarcina lutea* was introduced into tonsil crypts and cultures were made immediately, and after 10-minute, 1-hour, 24-hour and 48-hour intervals. The results are summarized in Table III.

Summary.—*Sarcina lutea* introduced in large amounts into tonsillar crypts could no longer be recovered after 24 hours, and even at the end of an hour the organisms had disappeared in two out of four cases. There seemed to be no tendency toward the development of a carrier state.

THE MECHANISM FOR DISPOSAL OF BACTERIA IN THE UPPER AIR PASSAGES

Despite the frequent presence of pathogenic bacteria in the upper air passages, both in health and in disease, it is clear that a highly effective mechanism is present in these localities which, except under extraordinary conditions, protects against invasion by foreign organisms. Were this not so, it is obvious that the spread of such organisms would soon become universal among the human race, with an attendant high incidence of disease. The effectiveness of this protective mechanism varies with various bacteria, and with the same bacteria at various times, as illustrated by the epidemiological facts of human disease. The details, however, of its action in particular instances of infection have not been completely worked out. A survey of the literature discloses studies on a number of factors which probably combine in making up the complex protective mechanism of the upper air passages. These factors may be classified as: (1) Mechanical (including the flushing action of secretions with the associated acts of swallowing and the ejection of nasal and mouth secretions); (2) chemical (including the effects of the reaction of the mouth and nose secretions with other possible bacterial inhibitory factors); and (3) biological (including such processes as phagocytosis and the effect of bacteria already present on the invader). These factors can be most conveniently discussed from a topographical standpoint.

The Conjunctiva.—Maxcy¹ states that the lachrymal secretion has no bactericidal action. Stort² found that colon bacilli instilled into the conjunctival sac of rabbits could no longer be recovered in culture after one hour. If the lachrymal duct were tied, the bacteria persisted in the conjunctiva for a much longer time. He concludes, therefore, that the organisms are swept rapidly into the duct, and that the mechanism for preserving the normal sterility of the eye—at least in the case of the organism studied—was a mechanical one, and not dependent on bacterial inhibitory action of the secretions. Maxcy³ was able in man to recover *B. prodigiosus* from the nose within five minutes after it had been introduced into the conjunctival sac.

The Nasal Passages.—Although the nasal secretion is normally scant, still the mucous surfaces are constantly moistened. The cilia of the epithelium and the secretion of the mucous membranes and that discharged into the nose from the lachrymal duct create a steady current toward the posterior nares.⁴ Furthermore, the configuration of the nasal cavities is such that bacteria and foreign particles are for the most part arrested near the anterior nares. Thus, cultures made in normal individuals yield large numbers of organisms

TABLE I.—FATE OF SARCINA LUTEA SWABBED ON THE TONGUE

Number of colonies of <i>Sarcina lutea</i> per plate recovered from tongue and pharynx																		
Date	Name	Diagnosis and condition	Age	Procedure	Immediately		After 10 min.		After 1 hr.		After 24 hrs.		After 48 hrs.		Control culture before inoculation		Remarks	
					Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx		
June 10.	M.	Cardiac, compensated. Mouth in average condition. Scarred tonsils.	50	1/2 slant S. L. swabbed on anterior half of tongue.	∞	Plate almost pure S. L.	60	1	8	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	Took nothing by mouth until after 1-hour culture.	
June 10.	G.	Tuberculous polyserositis. Mouth clean. Ragged tonsils.	15	1/2 slant S. L. swabbed on anterior half of tongue.	50	2	6	No S. L.	7	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	Took small amount of liquid between second and third cultures.	
June 8.	Mo.	Cardiac, compensated. Mouth in average condition.	60	1/2 slant S. L. swabbed on anterior half of tongue.	∞	Almost pure plate.	150	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	Took small amount of water between second and third cultures.	
May 31.	H.	Cardiac, compensated. Mouth in average condition.	30	1/2 slant S. L. swabbed on anterior half of tongue.	∞	Plate almost pure.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.		
May 31.	L.	Cardiac, compensated. Mouth in average condition.	50	1/2 slant S. L. swabbed on anterior half of tongue.	∞	Plate 1/2 S. L.	A few cols. S. L. (confluent).	4	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.		
May 31.	D.	Nephritis. Mouth in average condition.	40	1/2 slant S. L. swabbed on anterior half of tongue.	∞	Plate almost pure.	1	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	Took water between second and third cultures.	

TABLE II.—FATE OF SARCINA LUTEA SWABBED ON NASAL MUCOSA

Date	Name	Diagnosis and condition	Age	Procedure	Number of colonies of sarcina lutea per plate recovered from nose and nasopharynx										Control culture before inoculation	Remarks
					Immediately		After 10 min.		After 1 hr.		After 24 hrs.		After 48 hrs.			
					Nose	Nasoph.	Nose	Nasoph.	Nose	Nasoph.	Nose	Nasoph.	Nose	Nasoph.		
June 23.	G.	Abdominal aneurism. Nose and mouth normal.	38	1/2 agar slant of S.L. swabbed on nasal septum.	∞	No S. L.	∞	No S. L.	∞	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	Took nothing by mouth until after the 1-hour culture.
June 23.	H.	Cardiac, compensated. Nose and mouth normal.	60	1/2 agar slant of S.L. swabbed on nasal septum.	∞	No S. L.	∞	No S. L.	∞	No S. L.	7	No S. L.	No S. L.	No S. L.	No S. L.	Took nothing by mouth until after the 1-hour culture.
June 21.	T.	Cardiac, compensated. Nose and mouth normal. Scarred tonsils.	55	1/2 agar slant of S.L. swabbed on nasal septum.	∞	No S. L.	2	No S. L.	6	6	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	Drank water after the 10-minute culture.
June 21.	F.	Cardiac, compensated. Nose and mouth normal. Large scarred tonsils.	12	1/2 agar slant of S.L. swabbed on nasal septum.	∞	No S. L.	3	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	Drank water after the 10-minute culture.
June 19.	B.	Psychoneurosis. Nose and mouth normal.	20	1/2 agar slant of S.L. swabbed on nasal septum.	∞	No S. L.	∞	No S. L.	10	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	No S. L.	Took nothing by mouth until after the 1-hour culture.

at the nasal orifices and few or none from the deeper nasal passages.⁴ Maxcy¹ recovered *B. prodigiosus* from the nasopharynx 15 minutes after instilling it into the conjunctiva, and we found *sarcina lutea* in the pharynx 10 minutes after swabbing it on the anterior part of the septum.

With regard to the bacterial inhibitory effect of the nasal secretions, the literature is contradictory, some writers finding a marked inhibitory action and others failing to do so. Variations in the method of collecting and diluting the secretions, in the organism used, and in the method of plating, may account for these discrepancies. Kligler⁶ has shown recently that small amounts of nasal secretions added to culture media at times promoted the growth of organisms such as meningococci. He believes this action to be due to "vitamins." The experiments of Calvino,⁸ however, which approximate most closely natural conditions, indicate that the nasal mucosa is an unfavorable medium at least for some types of organisms.

It seems clear, therefore, that the normal tendency is to preserve sterility of the deeper nasal passages and that no true permanent nasal flora exists.

The Mouth and Throat.—The mouth affords an especially favorable opportunity for some types of bacterial growth; food particles, carious teeth, desquamated epithelium and saliva furnish media whose effectiveness is attested by the enormous numbers of bacteria constantly present even in so-called clean and well-kept mouths. There is, however, a continuous shift in the "normal" flora, so that cultures made from the same individual on successive days may yield different quantitative and qualitative results. Such variations are to be expected with changing food and fluid intake and variations in mouth hygiene. Furthermore, the abundant salivary and mouth secretions with the constant flushing effect of ingested fluids, swallowing and expectoration, undoubtedly constitute a cleansing mechanism.

With regard to the bacterial inhibitory effect of saliva and mouth secretions *in vivo*, no satisfactory data are at hand, although numerous test-tube experiments are on record. Thus, Sanarelli⁷ found that streptococci, staphylococci, *M. tetragenus* and *cholera spirilla* were rapidly destroyed by fresh filtered saliva *in vitro*, unless an enormous number of organisms were used. The pneumococcus, on the other hand, thrived in saliva better than in broth. Barnes⁹ using a similar method, found that saliva had no bactericidal action on streptococci or pneumococci. Variations in the results of such experiments are to be expected under various experimental conditions.

The importance of the normal mouth flora in over-growing and suppressing invading pathogenic organisms is indicated only in an indirect way. On artificial media, meningococci, pneumococci and influenza bacilli grow well in certain proportions with the normal mouth organisms. They may, however, be rapidly overgrown by "spreaders," particularly of the aerobic spore-bearing types. It is possible that such organisms may actually exert a similar effect in the mouth, although this is not directly demonstrated.

It is clear, therefore, that a complex mechanism exists in the upper air passages, which under certain conditions suffices to dispose of invading pathogenic microorganisms. The details of its operations are obviously variable, and as is to be expected, it often breaks down. Thus, such factors as dosage of the organism, local pathological processes or anatomical anomalies, variations in the biological activities of the organisms themselves, may play a part in explaining why certain bacteria may gain a foothold at one time; and at another, or in a different individual, be promptly wiped out. From the standpoint of epidemiology it seems more profitable, therefore, to observe the actual fate of organisms introduced into the upper air passages than to try to analyze their exact method of disposal.

TABLE III.—FATE OF *SARCINA LUTEA* INTRODUCED INTO TONSILAR CRYPTS

Date	Name	Diagnosis and condition	Age	Procedure	Number of colonies per plate of <i>sarcina lutea</i> recovered from tonsil crypt					Control culture before inoculation	Remarks
					Immediately	After 10 min.	After 1 hour	After 2 hours	After 4 hours		
June 26.	C.	Syphilis. Nose and mouth essentially normal. Small, clean tonsils with sealed crypts.	35	$\frac{1}{2}$ agar slant of <i>S. L.</i> introduced into a tonsil crypt.	∞ (Almost pure plate.)	∞ (Almost pure plate.)	∞ (Almost pure plate.)	No <i>S. L.</i>	No <i>S. L.</i>	No <i>S. L.</i>	Took nothing by mouth until after the 1-hour culture.
June 26.	F.	Hodgkin's disease. Large, ragged tonsils.	30	$\frac{1}{2}$ agar slant of <i>S. L.</i> introduced into a tonsil crypt.	∞ (Almost pure plate.)	∞ (Almost pure plate.)	6	No <i>S. L.</i>	No <i>S. L.</i>	No <i>S. L.</i>	Took nothing by mouth until after the 1-hour culture.
June 25.	M.	Cardiac, compensated. Large, ragged tonsils with open crypts.	60	$\frac{1}{2}$ agar slant of <i>S. L.</i> introduced into a tonsil crypt.	8	No <i>S. L.</i>	No <i>S. L.</i>	No <i>S. L.</i>	No <i>S. L.</i>	No <i>S. L.</i>	Took nothing by mouth until after the 1-hour culture.
June 25.	Fl.	Tuberculous pericarditis. Large, scarred adherent tonsils.	15	$\frac{1}{2}$ agar slant of <i>S. L.</i> introduced into a tonsil crypt.	∞ (Almost pure plate.)	No <i>S. L.</i>	No <i>S. L.</i>	No <i>S. L.</i>	No <i>S. L.</i>	No <i>S. L.</i>	Took nothing by mouth until after the 1-hour culture.

None the less, an attempt was made to determine, at least approximately, the mechanism which led to the rapid disappearance of *sarcina lutea*. The reaction of the mouth secretions, the effect of mechanical cleansing, and bacterial inhibitory effects of the mouth secretions were studied.

1. *Effect of the Reaction of Mouth Secretions.*—Saliva and mouth secretions were collected from each of the patients inoculated with *sarcina lutea*. The mucous membranes were scraped with a large platinum loop, after which the patient expectorated the saliva which had accumulated in the mouth. The entire mixture was diluted with an equal amount of fresh, sterile distilled water, and the reaction immediately tested. The colorimetric comparison method, as now generally used in bacteriological work⁹ was employed with phenol-sulphonephthalein and alizarin as indicators. The pH of the various specimens is indicated in the following table (Table IV).

TABLE IV
pH OF SPECIMENS OF SALIVA FROM INDIVIDUALS INOCULATED WITH
SARCINA LUTEA

Name	pH of saliva immediately	pH after standing one hour
Mo.	5.9.....	5.9
G.	5.9.....	—
H.	5.9.....	—
F.	6.0.....	6.0
Mu.	6.0.....	—
L.	7.0.....	6.9
E.	7.0.....	7.0
D.	7.2.....	7.1
T.	7.2.....	7.0
Ho.	7.3.....	—
Gr.	7.4.....	7.1
Fl.	7.6.....	7.3
Mo.	7.6.....	—

The range of growth of *sarcina lutea* was next tested. Tubes of plain agar with reaction adjusted from pH 5.0— to 8.0+ were inoculated. *Sarcina* grew with equal luxuriance on all the tubes within this range. It seems clear, therefore, that the reaction of the mouth secretions cannot alone account for the disposal of *sarcina lutea*.

2. *Mechanical Influences.*—An attempt was made to ascertain to what extent the normal washing processes in the mouth

TABLE V
BACTERIAL COUNTS FROM TONGUE BEFORE AND AFTER IRRIGATING
MOUTH WITH SALT SOLUTION

Name	No. cols. from 1 loop of tongue scrapings before irrigation	No. cols. from 1 loop of tongue scrapings immediately after irrigation	No. cols. from 1 loop of tongue scrapings 10 min. after mouth irrigation
B.	1600	810	—
M.	—	—	—
		Plate contains about as many colonies as before.	—

serve to remove organisms present. The mouth was thoroughly rinsed with one liter of sterile salt solution. The patient cooperated in making this washing effective by churning the fluid in the mouth and scraping the tongue with the teeth. Such an irrigation would be expected to remove more organisms than the ordinary acts of swallowing and expectoration. The tongue was scraped with a large platinum loop just before and just after the washing and at subsequent intervals. The loop of scrapings was diluted and plated in a standard manner. In no case was it possible to reduce the bacterial count by more than 50 per cent, even by such exten-

TABLE VI. EFFECT OF SALIVA ON THE GROWTH OF SARCINA LUTEA

	Tube 1	Tube 2	Tube 3	Tube 4	Tube 5	Tube 6	Tube 7
One c.c. of loop from each tube portion containing 0.2 c.c. saliva	0.2 c.c. saliva	0.2 c.c. suspension S. L. + 0.2 c.c. salt solution	0.2 c.c. suspension of mixed mouth bacteria + 0.2 c.c. suspension S. L.	0.2 c.c. saliva + 0.2 c.c. suspension S. L.	0.2 c.c. saliva + 0.1 c.c. suspension S. L.	0.2 c.c. saliva + 0.05 c.c. suspension S. L.	0.2 c.c. saliva + 0.025 c.c. suspension S. L.
Immediately	About 500 cols. of various kinds	— cols. S. L.	— cols. S. L. with about 50 cols. mouth bacteria.	— cols. S. L. with a few mouth bacteria.	— cols. S. L. with a few mouth bacteria.	250 cols. S. L. Mouth bacteria.	100 cols. S. L. Mouth bacteria.
15 minutes	About 300 cols. of various kinds.	— cols. S. L.	— cols. S. L. with about 50 cols. mouth bacteria.	About 1 as many colonies S. L. as in previous plate, with a good many mouth bacteria.	10 cols. S. L. appeared after 48 hours. Mouth bacteria.	No S. L. Mouth bacteria.	1 col. S. L. (appeared after 4 days) Mouth bacteria.
1 hour	About 500 cols. of various kinds.	— cols. S. L.	— cols. S. L. with about 100 cols. mouth bacteria.	2 cols. S. L. appeared after 48 hours. with a good many mouth bacteria.	1 col. S. L. appeared after 4 days. Mouth bacteria.	No S. L. Mouth bacteria.	7 cols. S. L. (appeared after 3 days).
2 hours	About 200 cols. of various kinds.	— cols. S. L.	— cols. S. L. with about 100 cols. mouth bacteria.	No S. L. Mouth bacteria.	No S. L. Mouth bacteria.	No S. L. Mouth bacteria.	No S. L. Mouth bacteria.
24 hours	About 500 cols. of various kinds.	— cols. S. L.	— cols. S. L. with about 100 cols. mouth bacteria.	No S. L. Mouth bacteria.	No S. L. Mouth bacteria.	No S. L. Mouth bacteria.	No S. L. Mouth bacteria.

sive irrigation. It seems, therefore, that mechanical processes alone cannot adequately account for the rapid disappearance of *sarcina lutea*. Table V shows an illustrative protocol.

3. *The Inhibitory Effect Upon Bacteria Exerted by the Mouth Secretions and Saliva*.—An attempt was made to reproduce the conditions present in the mouth as nearly as possible by the following method. 0.2 c. c. of fresh saliva was placed in each of a series of tubes. To each was added decreasing amounts of a thick suspension of *sarcina lutea*. One standard loop of the mixture of saliva and *sarcina lutea* was removed from each tube immediately and at various intervals, and plated on plain agar plates. The results which coincided in numerous experiments with various specimens of saliva, except as to slight quantitative variations, are illustrated by the following typical protocol (Table VI).

From this protocol, the following facts are apparent:

1. Cultures made from a specimen of saliva at various intervals up to 24 hours yielded about the same number and kind of organisms.

2. Cultures made at various intervals up to 24 hours from a suspension of *sarcina lutea* in salt solution yielded the same number of colonies.

3. Cultures made at various intervals up to 24 hours from a mixed suspension of mouth flora and of *sarcina lutea* yielded the various organisms in about the same proportions. *Sarcina lutea* was not overgrown or inhibited.

4. Cultures made at intervals up to 24 hours from suspensions of varying concentration of *sarcina lutea* in saliva yielded rapidly decreasing numbers of colonies of *sarcina lutea*. The number was much reduced in 15 minutes, only an occasional organism could be recovered after 1 hour, and none after 2 hours. Furthermore, the growth of the few organisms obtained after the first culture was inhibited for intervals of 1 to 4 days before the colonies appeared in the plates.

Smears were made from each tube in the above experiment at 15-minute, 1-hour and 2-hour intervals. After 15 minutes, abundant *sarcinae* were seen in all tubes. They were normal in staining qualities and in grouping. After 1 hour the smears from the mixtures of saliva and *sarcina lutea* showed the *sarcinae* to stain poorly and to be pale and gran-

ular. After 2 hours few definite organisms could be seen. No agglutination was apparent. The organisms from the control tubes stained normally.

It may be concluded, therefore, that saliva exerts a rapid bactericidal effect on this organism and that this effect is independent of the bacteria normally present in the saliva.

DISCUSSION

The general result of these experiments indicates that even after a short period of time it is usually impossible to recover *sarcina lutea* swabbed in large amounts on the tongue, nasal mucosa, or into the crypts of the tonsils. Disappearance from the nose was somewhat slower than from the other sites; in only one instance could any organisms be recovered after 24 hours, and in no case after two days. Cultures made in this way do not, of course, prove the complete absence of the organism in the mouth and nose, but the general trend of the quantitative relations indicates a rapid disappearance. The fact that the estimated dose of 50 to 100 billion organisms was vastly greater than that in any natural infection, indicates the remarkable efficiency of the mechanism present in the upper air passages for disposing of this organism. An analysis of the possible factors active in effecting this disposal indicated that reaction of mouth secretions, mechanical cleansing, and the mouth bacteria play little if any part, but that the saliva and mouth secretions exert a prompt and marked bactericidal effect.

Similar methods are being used in studying the fate of other organisms introduced into the upper air passages.

REFERENCES

1. Maxcy, Kenneth F.: *Journal A. M. A.*, 1919, LXXII, 636.
2. Stort, A. G.: *Arch. f. Hyg.*, 1891, XIII, 395.
3. Piersol, G. A.: *Human Anatomy*, 1906, p. 1416.
4. Hasslauer: *Centralbl. f. Bakteriologie*, 1906, 1. Abt., Ref. Bd. XXXVII, p. 1.
5. Kligler, I. J.: *Jour. Exp. Med.*, 1919, XXX, 31.
6. Calvino, V. E. M.: *Arch. Italiano di otologia, etc.*, 1899, VIII, 169.
7. Sanarelli: *Centralbl. f. Bakteriologie*, 1891, 1. Abt., X, 25.
8. Barnes, B. S.: *Trans. Chicago Path. Soc.*, 1907-09, VIII, 249.
9. Clark, W. M., and Lubs, H. A.: *Jour. Bacteriology*, 1917, II, 1.

THE INFLUENZA BACILLUS IN PARANASAL SINUS INFECTIONS

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There is some difference of opinion as to the nature of the organism primarily responsible for the influenzal epidemic of 1918-1919. Pfeiffer's bacillus was found in a sufficient number of cases to raise the question as to whether it was the primary agent, or, like the streptococcus and pneumococcus, a secondary invader.

We were interested to determine whether or not this bacillus occurred more frequently in a series of infected nasal sinuses observed immediately following the epidemic, than

in a series of such cases observed during a period when there was no epidemic. During the height of the epidemic in Baltimore, it was impossible, owing to the press of work, and the scarcity of skilled help, to make bacteriological examinations of the infected sinuses. Within six weeks after the epidemic had subsided, however, one of us (Neville) undertook a careful bacteriological study of every case of maxillary sinus infection treated at The Johns Hopkins Hospital. We limited our study to the maxillary sinus, because this cavity is the

one most frequently affected, and because the material for culture can be obtained from this situation with less risk of contamination than from the ethmoidal, frontal or sphenoidal cells.

We present for comparison two series of cases. The first series of seventy includes every case of accessory nasal sinus infection treated at The Johns Hopkins Hospital during the years 1912-1918, in which we have a report on the cultures made from the antrum.* Of these 70 observations, made during a period when there was no epidemic of influenza, we have 15 cases in which the influenza bacillus was found in the antrum. The 30 cases of the second series were all observed during February, March and April of 1919. In eight of these cases we found *B. influenzae* in the antrum. It is of interest that the percentage of cases in which the influenza bacillus was found in the antrum is about the same in each group.

The material for culture is obtained by a very simple method. A small piece of cotton on the end of a steel applicator is moistened with a 20 per cent solution of cocaine and 1:1000 adrenalin. The excess of cocaine is removed by pressing the cotton between two layers of gauze; this will insure against symptoms of cocaine poisoning. A small piece of cotton moistened with cocaine and adrenalin is also placed between the anterior end of the inferior turbinate and the septum, and both are left in place for ten or fifteen minutes. A curved trochar, a small rubber ear syringe, a nasal speculum and a finger bowl are then boiled for at least five minutes. The patient's nose is cleansed of all visible discharge. The trochar is passed under the anterior end of the inferior turbinate into the antrum, and the stylette removed. The patient bends 90° forward, and often the pus will drop from the cannula. If not, air or a few drops of sterile salt solution are blown into the antrum with the rubber syringe, and the material returning through the cannula is caught in a sterile test-tube. It is important that enough adrenalin be used to make the procedure absolutely bloodless, for we have found, in agreement with Rivers, that a few drops of blood mixed with the material obtained for culture will inhibit the growth of the influenza bacillus.¹

The bacteriological technique employed is as follows: The material is plated immediately on agar containing defibrinated rabbit's blood, and the plates are incubated at 37° C. for twenty-four hours. The various colonies are then examined in stained smears and transferred to blood-agar slants. After twenty-four hours the colonies showing the cultural characteristics of the streptococcus and pneumococcus are differentiated by Neufeld's bile soluble test. The pneumococci are grouped according to the method of Avery, Chickering, Cole and Dorchez.² The serum used was obtained from the

* It was formerly our custom to take cultures from infected sinuses (chiefly at operation) on cotton swabs. These swabs were sent to the regular bacteriological laboratory of the hospital but had often completely dried up before reaching the laboratory. This accounts for the comparatively small number in which we have a bacteriological report.

Rockefeller Institute. The influenza bacillus grows freely on blood-agar but not at all on plain agar. This differentiates it from the micrococcus catarrhalis. This latter organism may be differentiated from other gram-negative cocci by the use of Hiss's serum sugar media, and the Elser and Huntton classification.

In the first series of 70 cases observed during the period from 1912 to 1918, the influenza bacillus was found in the antrum in 15 cases (21 per cent). The streptococcus was found in 33 cases (47 per cent); in 10 of these the organism was hæmolytic. The pneumococcus occurred 12 times (17 per cent). The staphylococcus was found in 16 cases (22 per cent), in one of which it was hæmolytic; the proteus was found once; and the diphtheria bacillus twice.

In the second series of 30 cases observed during the three months immediately following the subsidence of the influenzal epidemic, the influenza bacillus was found in the antrum in eight cases (26 per cent). The streptococcus was again the predominating organism (14 cases, or 46 per cent); of these 14 cases, in four it was hæmolytic. The following organisms were occasionally found: the hæmolytic staphylococcus in four cases, the pneumococcus in three cases, the micrococcus catarrhalis in two cases, and a gram-negative diphtheroid bacillus in three cases. The diphtheria bacillus was found in one case, the bacillus lactis aerogenes once, and the proteus vulgaris in two cases.

The influenza bacillus was recovered from the antrum in pure culture in four cases. In four other cases it was found associated with other organisms: streptococcus hæmolyticus, streptococcus mucosus, micrococcus catarrhalis, micrococcus tetragenus, and the staphylococcus albus. The hæmolytic staphylococcus occurred four times, once in pure culture. The staphylococcus albus was found in eight cases, but was probably in each case a contamination from the nasal cavity.† The pneumococcus was recovered in three cases (in two Type III and in one Type IV), twice in pure culture, once mixed with a staphylococcus albus.

† The healthy nasal cavity is apparently a normal habitat for the staphylococcus albus. We took cultures from the middle turbinate in seven individuals with clinically normal nasal cavities. A little mucus was obtained from the middle turbinate with a platinum loop and implanted on plates of rabbit blood-agar. We found: staphylococcus albus 91 per cent; diphtheroids, 41 per cent; pneumococcus, Type IV, 16 per cent; micrococcus catarrhalis, 8.9 per cent.

Park and Wright, in 1898, took cultures with a platinum loop from far back in the nose and showed that the nasal secretion has no bacteriocidal action. Of 36 examinations only six were sterile. The predominating organism was the staphylococcus.

Hasslauer³ in 1902, made bacteriological examinations from the normal nasal cavities of 111 individuals. He found: staphylococcus in 25 per cent; pneumococcus in 20 per cent; streptococcus in 17 per cent; diphtheroid in 13 per cent.

He also investigated the bacteriological content of the nasal discharge in 78 cases with a coryza and found much the same varieties of organisms in both healthy and pathological nasal cavities. The only difference was that they were far more numerous in infected nasal cavities.

CONCLUSIONS

1. The influenza bacillus was found in infected maxillary sinuses in practically the same percentage (21 per cent) in a series of cases observed during a period of six years when there was no epidemic, as in a second series observed immediately following the epidemic in Baltimore during the winter of 1918-1919 (26 per cent).

2. The influenza bacillus is not infrequently found in pure culture in the antrum.

3. Clinically *B. influenza* is a pyogenic organism.

4. The predominating organism in all antrum infections is the streptococcus.

5. We infer from these observations that the influenza bacillus, like the streptococcus and pneumococcus, is a secondary invader, and not the primary cause of the disease known as influenza.

LITERATURE

1. Rivers, T. R.: The effect of different bloods on the growth of *B. influenza*. Johns Hopkins Hosp. Bull. Balto., 1916, XXX, 129-131. [*B. influenza* grows better on rabbit blood- and cat blood-agar than on human blood-agar; and defibrinated human blood and

normal human serum are very bactericidal for the strains of influenza bacillus studied as compared with defibrinated rabbit blood, normal rabbit serum and normal guinea-pig serum.]

2. Avery, Chickering, Cole and Dochez: Acute lobar pneumonia. Monogr. Rockefeller Inst. M. Research, N. Y., 1917, No. VII, p. 25.

3. Hasslauer, W.: Die Bakterienflora der gesunden und kranken Nasenschleimhaut. Centralbl. f. Bakteriologie, 1. Abt., Jena., 1902, XXXIII, 47-51.

Gibson, G. H., Bowman, B., and Connor, J. I.: Etiology of influenza, Brit. M. J., Lond., 1919, I, 331-335. [The influenza epidemic was due to a minute filtrable microorganism of coccoid shape grown by Noguchi's cultural methods.]

Lewis, C. T., and Turner, A. L. Suppuration in the accessory sinuses of nose: a bacteriological and clinical research. Edin. M. J., 1905, n. s., XVIII, 395-421; *ibidem*, 1910, n. s. IV, 293-318. [In 43 antral cultures taken without reference to an influenza epidemic the influenza bacillus was recovered three times. In another series of 57 cases it was recovered once. In both series streptococcus, pneumococcus and staphylococcus were the chief organisms found.]

MacCallum, W. G.: The pathology of the pneumonia in the United States army camps during the winter of 1917-1918. Monogr. Rockefeller Inst. M. Research, N. Y., 1919, No. X, 140. [Of 48 cases of pneumonia of influenza origin 16 contained the influenza bacillus in the bronchioles and occasionally in the alveoli. In six other cases the *B. influenza* was found in the sputum.]

MENINGOCOCCUS PNEUMONIA. I

THE OCCURRENCE OF POST-INFLUENZAL PNEUMONIA IN WHICH THE DIPLOCOCCUS INTRACELLULARIS MENINGITIDIS WAS ISOLATED. FROM OBSERVATIONS AT CAMP COETQUIDON, A. E. F., FRANCE

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Whatever may be the cause of primary influenza, it would seem that the secondary pneumonia may be caused by different organisms in different regions. As MacCallum¹ has pointed out, this variation "may depend on an endemic or epidemic distribution of organisms as inhabitants of the nasopharynx." Pneumococci,¹ streptococci² and staphylococci³ have been the most frequent secondary invaders and evidence now appears^{4, 5, 6, 7, 8} that the diplococcus intracellularis meningitidis (Weichselbaum) may produce fatal pneumonia. The cases reported in this paper were studied at Camp Hospital No. 15, Camp Coetquidon, Base Section No. 1, A. E. F., France, during the epidemic of influenza from September 1, 1918, to February 15, 1919.* Table I shows the total number of cases of influenza, pneumonia and cerebrospinal meningitis admitted to the hospital during this period.

* Prior to September 1, 1918, there had been but three deaths in this hospital due to the epidemic. They occurred in the last week of August, 1918. Cultures from the lung tissue at autopsy showed *B. influenza*, pneumococcus Type III and pneumococcus Type II, respectively. They are not included in this study be-

Prior to the outbreak of the epidemic of influenza, there were no cases of meningococcus meningitis in the hospital. It will be noted that coincident with the occurrence of meningococcus pneumonia, there occurred a considerable number of meningococcus meningitis cases.

The presence of influenza at Camp Coetquidon was first noted about September 1, 1918, and many cases of pneumonia

cause other data for comparison are not available. This study was terminated on February 15, 1919, because the evacuation of troops, begun at that time, rendered records for comparison unreliable and difficult to secure. On February 15, 1919, there were still eight cases in the hospital diagnosed as meningococcus pneumonia. These are included among the total cases recorded but their final disposition is not included.

Camp Coetquidon was an artillery training area occupied by troops which arrived from the United States during the latter part of August, September and October, 1918, and remained until February 15, 1919. These together with the permanent camp personnel numbered approximately as follows: September, 16,657; October, 19,177; November, 16,303; December, 12,850; January, 13,980; February, 14,780.

developed. On September 3, 1918, bacteriological cultures at autopsy from the lungs of a case of pneumonia showed a pure growth of meningococci (Type A Pasteur). A description of the bacteriological and serological technique employed is appended. On September 6, 1918, a similar case showed meningococcus Type B in the lung culture. Both cases occurred early in the epidemic, the patients were in the same ward at the same time, but the fact that different types of meningococci were isolated would seem to preclude the possibility of either of the two cases having been infected from the other or that both were infected from the same source.

On September 13 and 15 meningococci were recovered from the sputa of two pneumonia cases.

TABLE I

	Sept.	Oct.	Nov.	Dec.	Jan.	Feb. (4)	Totals
Cases of influenza admitted to hospital.	847	263	170	38	80	112	1510
Total cases of pneumonia admitted to hospital.	156	107	53	21	36	30	403
Total deaths from pneumonia.	27	30	12	0	3	6	78
Cases of pneumonia showing meningococci in sputum.	20	15	27	2	13	8	85
Deaths from pneumonia showing meningococci in lungs at autopsy.	6	5	6	0	1	5	23
Cases of meningococcus meningitis.	4	7	7	3	1	0	22
Deaths from meningococcus meningitis.	4	2	3	3	1	0	13

EXPLANATION OF TABLE I

Total cases of pneumonia include pneumonias due to all causes. Many cases admitted as influenza developed pneumonia after admission. Such cases are recorded as pneumonia and not influenza.

Cases of pneumonia showing meningococci are included among the total cases of pneumonia. This group, however, does not include any of the cases in which cerebrospinal meningitis was the primary disease.

Total deaths from pneumonia include all deaths from pneumonia. The deaths from pneumonia showing meningococci are included in this group.

Cases of meningococcus meningitis include all cases of cerebrospinal meningitis caused by meningococci, with or without pneumonia involvement.

It seemed, then, that the possibility of the meningococcus being an important factor in the epidemic was worthy of careful investigation. Cultures were therefore taken (September 19, 1918) from the throats of all respiratory cases in the hospital. Among 114 thus cultured meningococci (Type B Pasteur) were isolated from seven patients, six of whom had pneumonia.

On September 20, 22, 23, 25, 27 and 29 throat and sputum cultures of meningococci were recovered from 12 additional cases of pneumonia.

During the period studied, 78 cases of pneumonia came to autopsy. Cultures on blood agar were made from sections of the various parts of the affected lungs in all cases. The findings are of interest here for the purposes of comparing the frequency and the association of the various species of bacteria found during the epidemic. Meningococci were recovered from the lung tissue in a total of 23 cases (in pure culture in 7 cases and in mixed culture in 16). The complete bacteriological results in these 78 pneumonia autopsies are recorded in Table II.

The majority of the meningococci isolated were Pasteur Type B and were also agglutinated by Gordon's meningococcus sera, Types II and IV (corresponding to the Rockefeller Institute normal meningococcus). The cultural and serological findings in these cultures were confirmed at Base Laboratory No. 1 at St. Nazaire and at the Central Medical Laboratory at Dijon.*

In our experience, despite certain contradictory statements in the literature in regard to the correlation of the American, English and French classification of meningococcus types. Lieut.-Col. Gordon's Types I and III and the Rockefeller

TABLE II

BACTERIA ISOLATED FROM THE LUNGS AT AUTOPSY FROM 78 CASES OF PNEUMONIA AT CAMP HOSPITAL NO. 15, A. E. F., FRANCE

<i>B. influenza</i>	Meningococcus... 11 times
Pure cultures 7 cases.	Pneumococcus IV 7 times
*Mixed " 23 " , associated with	Strept. hemolytic. 6 times
Total " 30 " ,	Strept. vir. 1 time
	B. tuberculosis... 1 time
<i>Pneumococcus IV</i>	
Pure cultures 11 cases.	B. influenza... 7 times
*Mixed " 14 " , associated with	Strept. hemol. 4 times
Total " 25 " ,	Meningococcus ... 3 times
<i>Meningococci</i>	
Pure cultures 7 cases.	B. influenza... 11 times
Mixed " 16 " , associated with	Strept. hemol. 6 times
Total " 23 " ,	Pneumococcus IV 7 times
	Strept. vir. 1 time
	B. tuberculosis... 1 time
<i>Streptococcus hemolyticus</i>	
Pure cultures 9 cases.	B. influenza... 6 times
Mixed " 11 " , associated with	Pneumococcus IV... 4 times
Total " 20 " ,	Meningococci... 2 times
	B. tuberculosis... 2 times
<i>B. tuberculosis</i>	
Pure 0 cases.	Staphylococcus... 2 times
Mixed 6 " , associated with	Strept. hemolyt. ... 2 times
Total 6 " ,	Strept. vir. 1 time
	B. influenza... 1 time
<i>Streptococcus viridans</i> ...	2 cases
<i>Staphylococcus aureus</i>	2 "
<i>Pneumococcus I</i>	1 case
<i>Streptococcus mucosus</i>	1 "
<i>Bacillus aerogenes capsulatus</i> ...	1 "
<i>Staphylococcus albus</i>	1 "
	Associated with other organisms as indicated above

* Mixed cultures refer to two or more species of bacteria

Institute parnormal sera usually agglutinate the same cultures as Pasteur Type A. Colonel Gordon's sera II and IV and the Rockefeller Institute normal meningococcus serum usually agglutinate the same cultures as Pasteur Type B. Pasteur Types C and D are rare.

Gram-stained smears of the sputa from the pneumonia cases in which meningococci were isolated showed so many intracellular gram-negative diplococci as to resemble smears of spinal fluids from acute cases of meningococcus meningitis.

CLINICAL COURSE OF MENINGOCOCCUS PNEUMONIA

In the severe cases the onset was usually acute, after a period of indisposition lasting from a few days to a week. During the prodromal period there was generally a history of chills,

* Thanks are due to Captain E. H. Mason, M. C., U. S. Army, for assistance in confirming these cultures.

TABLE III

Case	Organization	Days in Hosp.	Laboratory findings during illness				Date of death	Autopsy findings		Autopsy number
			Urine	W. B. C.	Blood cultures.	Sputum cultures		Lung gross anatomy	Lung cultures	
V. F.	133 d F. A.	2	Alb. and casts	6400	Neg.	Mixed.....	9/3	Lobar pneumonia.....	Meningo. A.	25
T. R.	44th Engrs.	5	Alb. and casts	4400	Neg.	B. inf.....	9/6	Bronchopneumonia.....	Meningo. B.	28
J. B.	141st F. A.	12	7000	Neg.	Meningo. B.....	9/21	Bronchopneumonia.....	Meningo. B.	36
S. C.	114th T.M.B.	6	13,300	Neg.	Pneumo IV...	9/22	Bronchopneumonia.....	Meningo. B. Pneum. IV.	38
J. O'N.	61st Engrs.	7	7600	Neg.	B. inf.....	9/25	Lobar pneumonia. Sup.* bronchiolitis.	Meningo. B.	44
C. S.	141st F. A.	2	9/29	Lobar pneumonia.....	Meningo. B. Pneum. IV.	49
A. C.	141st F. A.	17	4400	Neg.	Meningo. B. diph- theroid.	10/3	Bronchopneumonia. Sup. bronchiolitis.	B. inf. Men- ingo. B.	57
M. D.	141st A. T.	7	9660	Neg.	Meningo. B.....	10/3	Lobar pneumonia.....	Meningo. B. Strept. vir.	58
R. S.	329th F. A.	6	9400	Neg.	Meningo. B.....	10/8	Lobar pneumonia.....	Meningo. B.	66
W. C.	329th F. A.	11	{ 6200 9600 }	Neg.	B. inf. Pneum. IV.	10/24	Bronchopneumonia. Sup. bronchiolitis.	B. inf. Men- ingo. B.	86
R. C.	328th F. A.	2	Alb. and casts	5400	Neg.	B. inf.....	10/27	Bronchopneumonia.....	B. inf. Men- ingo. B.	89
F. N.	329th F. A.	3	4200	Neg.	B. inf. Pneum. IV.	11/2	Bronchopneumonia. Wet lung.	B. inf. Men- ingo. A.	95
B. P.	Vet. Hosp.	3	Alb. and casts	2200	Neg.	B. inf.....	11/3	Bronchopneumonia. Wet lung.	B. inf. Men- ingo.	98
L. F.	330th F. A.	9	Alb. and casts	{ 2600 4200 }	Neg.	B. inf.....	11/4	Bronchopneumonia.....	B. inf. Men- ingo. C.	100
O. A.	113th A. T.	8	Alb. and casts	18400	Neg.	Meningo.....	11/9	Bronchopneumonia. Sup. bronchiolitis.	Meningo. Strept. hemol.	105
E. N.	Vet. Hosp.	11	Alb. and casts	8000	Neg.	Meningo.....	11/13	Bronchopneumonia. Sup. bronchiolitis.	B. inf. Men- ingo.	106
A. P.	131st F. A.	13	Alb. and casts	{ 9200 20,400 }	Neg.	B. inf. Meningo..	11/23	Empyema. Bronchopneu- monia. Sup. bronchiolitis.	B. inf. Men- ingo. Strept. hemol.	111
C. G.	133d F. A.	9	Alb. and casts	2200	Neg.	Meningo. B.....	1/29	Bronchopneumonia. Sup. bronchiolitis.	Meningo. B.	124
G. S.	133d F. A.	6	Alb. and casts	{ 11,200 25,000 }	Neg.	Pneum. IV. Men- ingo.	2/1	Bronchopneumonia. Sup. bronchiolitis.	Meningo. B. Pneum. IV.	125
A. J.	7th Vet. Hosp.	8	Alb. and casts	{ 5200 9600 }	Neg.	B. inf. Meningo- coccus	2/1	Bronchopneumonia. Sup. bronchiolitis.	Meningo. B.	127
J. D.	132d F. A.	3	Alb. and casts	7200	Neg.	Meningo. B.....	2/3	Bronchopneumonia. Sup. bronchiolitis.	Meningo. B. B. inf.	128
D. K.	705th M.T.C.	6	Alb. and casts	{ 1400 4400 }	Neg.	Meningococcus...	2/3	Lobar pneumonia.....	Meningo. C. B. inf.	129
R. L.	P. W. 38.	16	Alb. and casts	7800	Neg.	2/4	Bronchopneumonia. Sup. bronchiolitis.	Meningo. A. B. inf.	130

* Sup. Bronch. = Suppurative Bronchiolitis.

† Predominating organisms only are recorded under lung cultures.

fever, headache, cough, pain in the chest and general malaise. The skin was pale blue. The patient looked very toxic; the chest examination showed variable areas of dullness and numerous moist râles, quite generally distributed. A few cases showed distinct lobar consolidation. The temperature was 103°-106°, pulse 85-100, respiration 25-30. The urine showed albumin and casts, usually early in the disease. The blood findings were negative blood cultures and a normal or reduced white cell count. The sputum was at first thin and watery, but rapidly changed to a creamy white which, on microscopic examination, showed numerous pus cells and gram-negative diplococci. Severe cases grew rapidly worse; the cyanosis increased; the lung consolidation extended and the patient died within a few days. Among those who survived the first week, there appeared to be a marked tendency toward suppurative bronchiolitis and protracted recovery. As the areas of consolidation diminished, the bronchioles filled with thick muco-purulent secretions; marked emphysema frequently developed; such patients showed marked evidence of dysphonia. At this stage, there was usually a marked rise in the white cell count. Later in the disease, the meningococci in the sputum became considerably reduced and other organisms correspondingly more prominent.*

AUTOPSY FINDINGS IN MENINGOCOCCUS PNEUMONIA

The lung findings at autopsy were usually of the bronchopneumonic type with numerous points in the consolidated areas that exuded purulent fluid on pressure. Six cases were distinctly lobar in distribution. On section, the consolidated areas showed a peculiar pale violet color that appeared almost characteristic of meningococcus pneumonia. The pleura was generally quite free from exudate and the pleural surfaces were generally dry. Fibrinous pericarditis was present with very little increase of pericardial fluid. Endocarditis occurred in over half of the cases. Cloudy swelling of the liver, acute splenic tumor and parenchymatous nephritis were constant. The abdominal recti muscles were found ruptured in five cases. The upper bronchi were generally inflamed and covered with creamy pus. Meningococci were always found to be most numerous in the purulent exudate from the bronchioles. Cultures from the pericardium and pleural cavities never showed meningococci. One patient developed an empyema from which a pure culture of streptococcus hemolyticus was recovered from the fluid; yet, the lung cultures showed great predominance of meningococci. Meningococci were never recovered from any of the accessory sinuses. *B. influenzae* was recovered from the sphenoidal cells in pure cultures in four cases.

Table III shows the laboratory findings in the 23 fatal cases of meningococcus pneumonia (without cerebrospinal involvement).

That virulent meningococci were prevalent among the troops in Camp Cootenden is shown by the fact that from September

1, 1918, to February 15, 1919, 22 cases of cerebrospinal meningitis developed with 13 deaths. The meningococci isolated were of similar type to those found in the lung tissue of the meningococcus pneumonia cases.

BACTERIOLOGICAL FINDINGS IN CASES OF MENINGOCOCCUS MENINGITIS

Of the 22 cases of meningococcus meningitis that occurred during this period, blood cultures were taken in 16 with three positive results. The positive results were all obtained from early cases; and no positive blood cultures were obtained after the first day of the disease. In one case the spinal fluid was clear at the time the positive blood culture was secured. In this culture, the meningococci numbered 2 per c. c., yet on the following day, when the spinal fluid showed a high-cell count and numerous meningococci, a second blood culture gave negative results.

Spinal fluid cultures all gave positive results at the time the first turbid fluid was secured. In nearly all cases, however, cultures failed to grow meningococci after the third or fourth day, even though the white cell count remained high for much longer periods.

Panophthalmitis developed in one case and meningococci were recovered from the eye after enucleation. Among the 13 cases that came to autopsy, meningococci were recovered from the ventricles or base of the brain in six and from the pericardium in two cases. There was distinct evidence of pneumonic involvement in ten cases, from which cultures from section of the involved lung showed meningococci* in six cases (four times alone and twice associated with *B. influenzae*). The other four cases gave lung cultures of streptococcus hemolyticus, pneumococcus Type IV, pneumobacilli and staphylococcus aureus, respectively. Eighteen meningococcus cultures, secured from cases of cerebrospinal meningitis that were typed, proved to be Type B Pasteur.

Meningococcus Carriers.—During the progress of the epidemic, efforts were made to segregate the carriers of meningococci in the various organizations that were showing the greatest number of cases. The carrier rate varied greatly at different times and in different barracks at the same time, the general rate being much higher early in the epidemic than later. Some of these carrier surveys were made on groups of men too small to furnish reliable figures. But four surveys were made at different times on fairly large numbers of men as follows:

Time	Number of men cultured	Carriers found	Percentage
Sept. 20/18	1460	168	16
Oct. 20/18	2284	280	12
Dec. 6/18	1534	110	8
Feb. 10/18	1496	60	5

These figures are of interest because they show an unusually high meningococcus carrier rate while the epidemiological waves were at their highest. The greatest number of carriers generally appeared to be present in the barracks where

* Thanks are due Captain W. M. Rhett, M. C., and the Medical Staff of Camp Hospital No. 15 for much of the clinical data.

respiratory affections were most numerous. Carriers isolated were recultured twice each week. Very few of them continued to be carriers over prolonged periods and no so-called "permanent carriers" were found during the investigation.

DISCUSSION

It will be observed that in this series meningococci rank third among the bacteria found most frequently in the lungs at autopsy in cases of pneumonia, being exceeded only by pneumococci and *B. influenzae*. However, if cerebrospinal meningitis cases be included, the meningococcus becomes the most frequently found organism in the lesions causing death during the epidemic. Out of 50 strains of meningococci typed from carriers selected at random 44 were Type B, four Type C, and two Type A Pasteur. Eighteen cases of cerebrospinal meningitis were caused by Type B meningococcus. Nineteen autopsy cultures from cases of meningococcus pneumonia showed 14 Type B, three Type A, and two Type C Pasteur. It is, therefore, evident that the prevailing type of meningococcus during this period was Type B Pasteur and was responsible for all of the meningitis cases as well as the larger proportion of meningococcus pneumonia cases. The frequent association of meningococci with *B. influenzae* is of special interest. On artificial media, the two organisms grow together exceedingly well. The possibility of a symbiotic pathogenicity of these organisms is worthy of further study.

CONCLUSIONS

1. That meningococci were an important factor in the causation of post-influenza pneumonia at Camp Coetquidon, from September 1, 1918, to February 15, 1919.
2. That the meningococci present in the lungs in cases of meningococcus pneumonia were essentially the same type of organisms as those found in the spinal fluids in cases of epidemic cerebrospinal meningitis.
3. That cases of meningococcus pneumonia may arise from contact with cases of meningococcus cerebrospinal meningitis and *vice versa*.
4. The meningococci may produce either bronchopneumonia or lobar pneumonia.

TECHNIQUE OF BACTERIOLOGICAL EXAMINATIONS

Blood Cultures.—Routine blood cultures were made on all cases of pneumonia. The medium used for such routine cultures was prepared as follows: Peptone, 10.0; salt, 5.0; glucose, 5.0; beef infusion, 1000.0. This was titrated to +0.4 acidity to phenolphthalein; tubed in large test-tubes and sterilized in an autoclave at 30 pounds for 15 minutes.

Blood for culture was drawn from one of the arm veins with a sterile 10 c.c. syringe. This amount of blood was then injected into 40 c.c. of medium after which the mixture was incubated for 72 hours, unless growth occurred earlier. This method gave good results with pneumococci, streptococci and *B. influenzae*, but trial cultures with meningococci were unsatisfactory.

Blood cultures for meningococci were made on a medium prepared by adding 2 per cent agar to the above-mentioned bouillon and sterilizing as before. This medium was melted and cooled to 45° C. The amount of blood drawn for each culture was 10 c.c. as before. This was mixed with 30 c.c. of the melted medium and poured into sterile petri dishes, allowed to set and placed inverted in the incubator for 72 hours unless growth occurred earlier.

Cultures of spinal fluids and sputa were made on a petri dish medium prepared by adding 2 per cent of fresh sterile human blood (kept fluid by citration) to the previously mentioned agar medium, after melting and cooling to 50° C. This was poured into sterile petri dishes and allowed to set. Spinal fluids were collected in sterile test-tubes and centrifuged. Preliminary examinations were made by microscopic examination of smears stained by Gram's method. Cultures were made by smearing the centrifuged sediment over the surface of the blood agar plates and incubating over night.

Sputa were obtained by having the patient cough and collecting the material directly into a sterile petri dish, from which direct smears were stained by Gram's method and examined. Cultures from sputum were made by selecting representative portions, smearing on blood-agar plates and incubating over night.

Agglutination Tests.—The sera used for preliminary agglutinations were Lederle's and the Rockefeller polyvalent anti-meningococcus serum. The sera used for type determinations were Pasteur Institute Types A, B and C. All routine agglutinations were read macroscopically. The standard dilution was 1:50. Colonies resembling meningococci were smeared and stained by Gram's method and if found to be gram-negative diplococci, agglutination tests were made with standard sera. Subcultures, whenever necessary, were made by subculturing suspicious colonies either on Loeffler serum tubes or on blood-agar plates. The suspected colonies were emulsified with normal saline and this emulsion was mixed in equal proportion with polyvalent antimeningococcus serum diluted 1:25 with normal saline. A control tube containing normal saline instead of the antimeningococcus serum was set up in each case. In the early part of our work, control tubes made with normal horse serum were also set up. Later, these were discarded. The tubes containing the above mixtures were incubated for four hours at 37° C.

Positive cases were typed by substituting Pasteur Institute antimeningococcus sera A, B and C for polyvalent serum, using the same dilutions, controls and temperature of incubation as used for the preliminary agglutinations.

REFERENCES

1. MacCallum, W. G.: *Journal A. M. A.*, March 8, 1919, LXXII, 720-23.
2. Chickering, H. T., and Park, J. H., Jr.: *Jour. A. M. A.*, March 1, 1919, LXXII, 617-626.
3. Jacobitz: *Zeitschr. f. Hyg.*, 1907, LVI, 175-192.
4. Gordon, M. H. (Temp. Hon. Lt.-Col. R. A. M. C.): Personal communication.

5. A few cases of pneumonia in which meningococci have been isolated have been reported in army cantonments in the U. S. A.

6. Fletcher, W.: *Lancet*, Jan. 18, 1919, I. No. 3, 104. Meningococcus bronchopneumonia in influenza.

7. Kinnicutt, R., and Binger, C. A. L.: *Am. Jour. Medical Sciences*, Sept., 1919, CLVIII, No. 3, 360-369. Isolation of the meningococcus from cases of so-called influenza.

8. Meader, F. M., Means, J. H., Hopkins, J. G.: *Am. Jour. Medical Sciences*, Sept., 1919, CLVIII, No. 3, 370-397. "Account of an Epidemic of Influenza Among American Troops in England."

9. Osler, W.: *Principles and Practice of Medicine*, 8th ed., p. 113. "This was found in eight of the Boston cases and in one it was so extensive that it could have been mistaken for the ordinary croupous pneumonia."

MENINGOCOCCUS PNEUMONIA. II

THE EPIDEMIOLOGY OF POST-INFLUENZAL PNEUMONIA IN WHICH THE DIPLOCOCCUS INTRACELLULARIS MENINGITIDIS WAS ISOLATED. FROM OBSERVATIONS AT CAMP COETQUIDON, A. E. F., FRANCE

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Because of the occurrence of the cases of meningococcus pneumonia described in the preceding paper,¹ the Base Surgeon, Base Section No. 1, A. E. F., France, requested us to investigate the epidemiology of this condition.

This study includes all of the bacteriological examinations made at Camp Hospital No. 15, Camp Coetquidon, A. E. F.,

every new patient at the time he was received into the hospital; (2) from all patients and attendants in the hospital; (3) from all patients at the time of their discharge from the hospital, and (4) from all contacts of recent cases of meningococcus meningitis in the barracks.

Until their cultures were reported negative, patients were held in strict quarantine in special wards of the hospital and discharged patients and contacts were held in "working quarantine" in the barracks, i. e., they could drill and mingle with other troops out of doors but had to sleep in isolated barracks.

In all, 1573 different patients, attendants, and contacts were cultured. Cultures were repeated at three-day intervals on all men found harboring meningococci until two successive negative cultures were obtained.

In Table I the results of these cultures are summarized.

The numbers of cases of cerebro-spinal meningitis and pneumonia from which meningococci were recovered and the number of carriers found in each organization as a result of the surveys of patients in hospital and of contacts in barracks are indicated in Table II.

SUMMARY

From the necropsy and cultural investigations described in the preceding paper (Meningococcus Pneumonia I), there can be no doubt that the post-influenzal pneumonia in Camp Coetquidon was due in at least 23 cases to infection with the meningococcus. This conclusion is further substantiated by the epidemiology. The 140th, 141st and 142d brigades of field artillery came from Camp Beauregard (Louisiana) in which numerous cases of cerebrospinal meningitis (meningococcal) had occurred during the previous winter. Probably many men of these organizations still harbored meningococci in their throats. The epidemic of influenza with its coughing greatly increased the number of these meningococcus carriers.

TABLE I

Situation of men examined	Number of men cultured	Number found positive, i. e. with meningococci in the rhinopharynx	Percentage of positive or carrier rate
Receiving wards	102	8	8 per cent.
Other hospital wards	456	32	7 per cent.
Discharged patients	596	85	14 per cent.
Contacts in barracks of 141st Field Artillery	261	38	14 per cent.
Contacts in barracks of 142d Field Artillery	86	8	9 per cent.
Contacts in barracks of 114th Trench Motor Battery	66	13	20 per cent.
Contacts in barracks of 114th Ammunition Train	6	0	0 per cent.
Total	1573	184*	12 per cent.

* The great majority of these carriers were of the temporary class. Of 167 meningococcus-positive patients on the third day only 35 were found positive. Of 165 carriers at the same examination the sixth day only 12 were positive.

France, of contacts of meningococcus pneumonia and meningococcus meningitis cases during the latter part of September and the early part of October, 1918.

In order to determine whether the incidence of these cases was due to contact or infection in the hospital or in the barracks, cultures from the rhinopharynx were taken: (1) from

¹ See p. 324 of this issue.

The cultural surveys of the hospital patients and barrack contacts (Table I) show an average meningococcus carrier rate of nearly 12 per cent. From the wide distribution, as shown

TABLE II

Organization	Number of meningococcus pneumonia cases	Number of meningococcus meningitis cases	Number of meningococcus carriers found while patients in hospital	Number of meningococcus carriers found in survey of barrack	Total number of meningococcus carriers found in each organization
131st Field Artillery.	5	0	3	No survey.	3
132d F. A.	1	0	3	No survey.	33
133d F. A.	2 (1 fatal).	0	5	No survey.	5
140th F. A.	3 (1 fatal).	0	12	No survey.	12
141st F. A.	5 (4 fatal).	4 (1 fatal).	34	33	72
142d F. A.	0	2 (2 fatal).	10	8	18
328th F. A.	1	0	1	No survey.	1
329th F. A.	1 (fatal).	0	14	No survey.	14
330th F. A.	0	1	2	No survey.	2
114th Ammunition Train.	1 (fatal).	1	29	0	29
310th A. T.	0	0	2	No survey.	2
114th Trench Mot. Bat.	1 (fatal).	1 (fatal).	0	13	13
61st Engineers.	2 (1 fatal).	0	3	No survey.	3
Casuals...	1 (fatal).	0	7	No survey.	7
Total...	23 (11 fatal).	9 (4 fatal).	125	59	184

in Table II, it was impossible to state definitely whether the infections occurred after the patients were received into the hospital or whether they had occurred in the barracks, but it is probable from the high carrier rates in both places that the influenza patients might well have acquired their secondary infection in either location.

It would seem evident, therefore, that the meningococcus was both endemically and epidemically distributed in the rhinopharynges of the troops in Camp Coetquidon and that this explained the relatively large number of cases of post-influenzal pneumonia in which meningococci were isolated.

TECHNIQUE USED IN EXAMINATION OF MENINGOCOCCUS PNEUMONIA AND MENINGITIS CONTACTS

Swabs were taken from the posterior rhinopharyngeal wall (curved wire swab "A" and tongue depressors "B" being used) and immediately inoculated on a small area of a hemolysed blood-agar plate. (Veal infusion agar + 0.2 per cent to phenolphthalein, or Ph. 7.8 was used; 3.0 c. c. of human, sheep, or rabbit's blood, hemolysed with 10 c. c. of sterile distilled water, were added to each 100 c. c. of melted agar at 50° C., immediately before pouring plates). This inoculation was then spread over the whole surface of the plate by means of a sterile wire spreader (C), (either immediately or on return to the hospital laboratory) and the plates incubated for from 18

to 24 hours at 37° C. They were then examined for suspicious colonies with the naked eye or a 10-power hand-lens. Meningococcus colonies are round, transparent, light gray and not umbilicated. Suspicious colonies were fished to hemolysed blood agar or Loeffler coagulated serum slants and incubated over night. A gram-stained smear was then made from each subculture.

Those containing gram-negative cocci were emulsified in normal saline as follows:

1. Saline was added to the cultures with a pipette according to the amount of growth (*i. e.*, 2 to 3 c. c.).

2. The growth was carefully washed off by means of a dropping pipette (*i. e.*, one fitted with a nipple) and transferred to a second tube.

3. Saline solution was added to these suspensions so that all were distinctly and equally cloudy.

4. The emulsions were agglutinated with meningococcus serum, the following technique being used: Five drops, or

TABLE III

To the 1st tube.	5 drops or 0.25 c. c. of the bacterial suspension.	5 drops or 0.25 c. c. Rockefeller Institute or N. Y. Board of health polyvalent meningococcus serum.	Previously diluted to 1:25.	Making the final dilution 1:50.
To the 2d tube.	" "	5 drops or 0.25 c. c. Pasteur type A meningococcus serum.	"	"
To the 3d tube.	" "	5 drops or 0.25 c. c. Pasteur type B meningococcus serum.	"	"
To the 4th tube.	" "	5 drops or 0.25 c. c. Pasteur type C meningococcus serum.	"	"
To the 5th tube.	" "	5 drops or 0.25 c. c. Pasteur type D meningococcus serum.	"	"
To the 6th tube.	" "	5 drops or 0.25 c. c. normal saline.	Control.	

0.25 c. c. of the bacterial suspension and the same quantity of various meningococcal type sera were placed in each of five agglutination tubes as indicated in Table III.

The five tubes were then incubated at 37° C. preferably for two hours in a water-bath or three hours in a dry incubator.

Lt. Col. M. H. Gordon's meningococcus type sera, I, II, III and IV or the Rockefeller Institute normal, paranormal, and intermediate type sera may be substituted for the Pasteur Institute type sera A, B, C and D.

When many cultures are to be agglutinated it will be found more economical of time and material if only tubes 1 and 6

are used. If after two hours there is positive agglutination with a polyvalent serum, the original suspension may then be typed by agglutinating in tubes 2, 3, 4 and 5.

The men whose cultures gave positive agglutination with a polyvalent serum were reported immediately as carriers, placed under hospital or working quarantine (*vide supra*), and re-

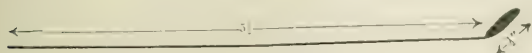


FIG. 1.

examined at three-day intervals until two successive negative cultures were obtained.

APPARATUS

A. Ordinary hay wire was cut into six-inch lengths and the distal half-inch was bent at an angle of 135° with the shaft. Non-absorbent cotton was twisted around this distal curved

end. These were sterilized by dry heat in lots of 25 in metal containers or glass jars, the tops of which were covered with paper. In our opinion, this swab is more convenient than the West tube swab not only on account of its greater simplicity of preparation but from the fact that any one with a little practice

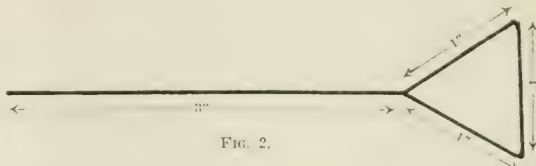


FIG. 2.

can swab the posterior rhinopharyngeal wall of an adult without touching the mouth structures.

B. It was found that requiring each man to use his own mess spoon as a tongue depressor was often convenient.

C. To make spreaders six-inch lengths of hay wire were bent as shown in the diagram. These were sterilized by dry heat in lots of 25 in metal or glass containers.

THE OCCURRENCE OF THE PFEIFFER BACILLUS IN MEASLES

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Certain similarities between measles and influenza were especially noticeable when these diseases were prevalent during the early part of last autumn. With the onset of influenza at Camp Devens, Mass., the symptoms in the earlier cases were distinctly less fulminating than at the height of the epidemic. The possibility of measles in the pre-eruptive stage required consideration in establishing the diagnosis of the first group of influenza patients admitted to the base hospital. The acute onset of conjunctival and respiratory symptoms was accompanied by a pronounced leucopenia. There are other noteworthy similarities between the two diseases. Both are highly contagious and are frequently complicated by pneumonia in its various forms. The occurrence of the Pfeiffer bacillus in a high proportion of patients has been reported in measles as well as influenza. As we were engaged at this time in the study of measles, it seemed advisable to investigate the occurrence of Pfeiffer and Pfeiffer-like organisms in measles patients.

Summary of Literature.—The literature contains fairly numerous reports of the occurrence of *B. influenzae* of Pfeiffer in cases of measles. Unfortunately a considerable number of the reports fail to furnish the information upon which the identification of the bacillus was based. In some, reliance seems to have been placed upon microscopic examination of smears stained by Gram's method; in other instances typical cultures were obtained upon blood-agar but no evidence was furnished to show that hæmoglobin was essential for successful

cultivation. Such results are open to doubt since other organisms may simulate closely the growth of *B. influenzae* on blood-agar. In the following review, as a rule, those papers will be omitted in which pneumonia and a Pfeiffer bacillus infection are reported as remote sequelæ of measles.

The association of measles and the influenza bacillus was first mentioned by Palttauf¹ in 1899. He reports the occurrence of *B. influenzae* in two cases of bronchopneumonia following measles; the details concerning the means of identification of the bacillus are not stated.

Giarrè and Picchi² were the first investigators to report the occurrence of Pfeiffer-like organisms in active cases of measles, pure cultures being recovered readily from the conjunctival and bronchial secretions. These authors raise the question of a possible specific etiologic rôle of these organisms in measles.

Albrecht and Ghon³ in 1901 describe one case of bronchopneumonia developing three weeks after an attack of measles. At autopsy the influenza bacillus was isolated from the lung.

In the autopsy of 23 cases of measles Jehle⁴ reports the occurrence of the Pfeiffer bacillus in the heart's blood in 15 and in the lungs in 18 cases. This author regards the influenza bacillus as a common secondary invader in the acute exanthemata.

Süsswein⁵ in 1901 studied measles patients clinically and at autopsy; he recovered the Pfeiffer bacillus in 10 of 21 cases. The positive cases were considered to be mixed infections of measles and influenza.

Lebecher⁶ in autopsies of 11 cases of measles, recovered the Pfeiffer bacillus in 3 cases from the lungs; his work is of especial interest in that two of three cases showed a pneumonia with the influenza bacillus present in pure culture.

Klienberger⁷ reports cultivation of "hæmophilic" bacilli from the conjunctivæ in 3 of 9 patients of measles during life, and in one of two cases at autopsy a pure culture of "hæmophilic" bacilli was obtained from the heart's blood.

Davis⁸ examined uncomplicated cases of measles during the stage of eruption. Cultures were taken from the sputum or from throat swabs, a single examination being made in each case. Organisms indistinguishable from the Pfeiffer bacillus were isolated in 13 of 22 cases.

Pacchioni and Franchioni⁹ obtained Pfeiffer-like organisms readily from the mucous membrane of measles cases. Careful blood cultures in 25 patients were negative for this organism in all except one case; one positive culture was obtained shortly before death from a case complicated by bronchopneumonia. These authors give serious consideration to the possibility that measles may be caused by a Pfeiffer-like organism.

Reiss and Gins¹⁰ report the cultivation of the influenza bacillus from the blood 17 days before death from a case of postmeasles bronchopneumonia.

Of especial interest are those reports which record the presence of the Pfeiffer bacillus in the uncomplicated cases of measles during life. The bacillus has been found, as a rule, only in the mucous membrane of the conjunctivæ and in the respiratory tract. Only rarely has it been recovered by blood culture and then only in cases complicated by pneumonia. It is noteworthy that Liebscher in 1903 reported the occurrence of the Pfeiffer bacillus in pure culture in the lungs in two fatal cases of pneumonia following measles.

EXPERIMENTAL WORK

The following examinations were conducted chiefly at Camp Devens, Mass., and were commenced immediately after the decline in the epidemic of influenza in September and October, 1918. The latter began on September 8, reached its maximum 8 days later and declined very rapidly during the next week. In the remainder of September and October a few cases were admitted practically every day; by the first of November the admissions for influenza had virtually ceased. Small foci of the infection probably remained in camp throughout the winter. A full account of the epidemic was reported by Woolley.¹¹ The measles patients were examined with the object of determining the relative frequency of Pfeiffer or Pfeiffer-like organisms and the period for which these organisms persisted after the subsidence of the symptoms of measles. Numerous cultures of hæmoglobin requiring organisms were isolated; these strains were, superficially at least, identical with *B. influenza* of Pfeiffer.

Technique.—The cases of measles were examined during the stage of eruption, the first examination being made as a rule within from 24 to 36 hours after the appearance of the rash; subsequent examinations were made at intervals of one to two weeks. Only a single examination was made during the eruptive stage in the cases which were negative. All of the patients showed the usual respiratory symptoms but only two of the cases were complicated with a definite pneumonia. As a routine the sputum of patients was examined, material being secured, as far as possible, which had been coughed up from the trachea or bronchi. In the hope of eliminating some of the commoner saprophytes, the sputum was injected in quantities of 0.25 to 0.5 c. c. intraperitoneally into white mice according to the technique recommended

by the Rockefeller Hospital for the isolation of the pneumococcus. The mice were sacrificed when they were markedly ill, usually after about 10 to 12 hours, spontaneous deaths being for the most part avoided. Cultures were made on blood-agar plates. Throughout this work human blood-agar has been employed—10 per cent blood in meat infusion agar with a reaction to phenolphthalein equivalent to 0.1 per cent of normal acid. These plates were inoculated from the peritoneal exudate, from the heart's blood and from any early pneumonic or hæmorrhagic patches in the lung.

The growth from the heart's blood and from the lung often showed an almost pure culture of Pfeiffer-like organisms, i. e., a small nonmotile Gram-negative bacillus (about 0.2 by 0.5 micron) without capsule or spore formation, growing aerobically on human blood-agar as minute discrete colonies without producing hæmolysis. The need for hæmoglobin was tested by substituting

TABLE I
INCIDENCE OF PFEIFFER-LIKE BACILLI IN SPUTUM OF MEASLES PATIENTS

Case number	Date of first examination	Period of observation			
		During eruptive stage	10 to 14 days after eruption	20 to 25 days after eruption	40 days after eruption
1	Nov. 12	Positive	Negative
2	" 12	"	Positive	Negative
3	" 12	"	Negative	Negative	"
4	" 12	"	"	"
5	" 12	"	"	"
6	" 12	"	"	Negative
7	" 26	"	Positive	"
8	" 26	"	"	Positive
9	" 26	Negative	Negative	"
10	" 26	Positive	"	"	Negative
11	" 26	Negative	"	Negative
12	" 26	Positive	"	"
13	" 28	Negative	"	"
14	" 28	Positive	"	"
15	" 28	"	Positive	Negative
16	" 30	Negative	"	"
17	" 30	Positive	Positive	Positive	Negative
18	" 30	"	"	Negative
19	" 30	"	Negative	"
20	" 30	"	"	"
21	" 30	"	"	"
22	Dec. 2	"	Positive	"
23	" 2	Negative	Negative	"
24	" 4	Positive	"	"
25	" 4	"	"	"
Total		Positive 19, or 79%	Positive 6, or 24%	Positive 6, or 26%	Positive none

ascitic fluid for blood in the culture medium—10 per cent of unheated ascitic fluid, free from bile pigments, with a specific gravity of 1.018. Blood serum was not employed on account of extremely minute amounts of hæmoglobin which may sometimes suffice for the growth of the Pfeiffer bacillus. In testing the hæmoglobin requirements of a given strain, blood and ascitic media were prepared from a common stock of agar. Heated blood-agar (chocolate-agar) was occasionally employed. Agar of the same composition as used for the fresh blood medium was mixed with human blood (10 per cent). The mixture was maintained at a temperature of about 95° C. for approximately ten minutes.

Strains of a Pfeiffer-like organism were recovered from five of the first six cases of measles that were examined. Seven normal men on duty at the base hospital were tested in the same way. Two of these men had had influenza 6 weeks before. No organisms resembling the Pfeiffer bacillus were found; these tests were repeated three and seven days later with nega-

tive results. The following table gives the incidence of the Pfeiffer-like organisms found in 25 additional cases of measles.

The cases in Table I are given in chronological order to show that the positive results occurring on the first examination were distributed rather equally throughout the series.

Distribution of the Pfeiffer-like Organisms.—Examinations were made for determining the extent to which the hæmoglobin requiring organisms are distributed throughout the body in cases of measles. Cultures for this purpose were made during the first day of the rash from the conjunctivæ, from morbillous lesions of the skin, from the blood and in two cases from lymphatic glands.

Conjunctivæ.—Inoculations from the inflamed conjunctivæ were made with a cotton swab on blood-agar plates. The secretions showed comparatively few bacteria of any kind. Fourteen cases were examined and Pfeiffer-like cultures were recovered from six; in two of these cases the organisms were present in relatively large numbers in almost pure culture.

Skin Lesions.—Small pieces of skin showing morbillous lesions were excised and smeared on blood-agar. Eight cases were examined but no hæmoglobin-requiring organisms were recovered.

Blood Cultures.—In view of the almost constantly negative results of blood cultures for the Pfeiffer bacillus in influenza, comparatively few examinations were made in the measles cases. Meat infusion broth containing a little laked human blood was inoculated with the patient's blood during the first 12 to 24 hours of the rash, from 1 to 5 c. c. of patient's blood with 75 to 100 c. c. of broth being used. Large Erlenmeyer flasks were employed as containers for the broth in order to give a large surface area. After incubation for 24 to 48 hours, subinoculations were made from these flasks on ordinary blood-agar and on heated blood-agar plates. The results in seven cases were negative. Six of these were uncomplicated. One patient developed early pneumonic lesions; the cultures were continued during the 2d, 3d and 4th day of the rash, but only a non-hæmolytic streptococcus was recovered from the blood.

Lymphatic Glands.—In a rather large number of the infectious diseases the causative organisms can be recovered from the lymphatic glands more readily than from the blood stream. In measles there is at least a theoretical possibility that the virus is disseminated by way of the lymphatic system. In two cases, a superficial gland was excised from the inguinal region as soon as the rash had advanced to this area. Smears from the gland were made on blood-agar and on heated blood-agar plates. The results in one case were negative; in the other, 5 or 6 colonies in all were obtained on the heated blood-agar, no growth developing on the unheated media. Subcultures were obtained either on heated or unheated blood media but only with difficulty; no growth was obtained on aseptic agar. Even on heated blood-agar the colonies were always much smaller than the typical Pfeiffer colonies; sometimes growth could be definitely demonstrated only by the microscopical examination of a stained smear. In its morphology and staining reactions, this organism corresponded to the Pfeiffer bacillus except that, even in very young cultures on unheated blood-agar, numerous

forms were present which were from two to four times the length of the typical Pfeiffer organism. After four sub-inoculations the strain died out.

COMPARISON OF PFEIFFER STRAINS FROM CASES OF MEASLES AND OF INFLUENZA

These strains of organisms from the conjunctivæ and the sputum were propagated on human blood-agar, transfers being made at intervals of four or five days. They were compared with similar strains of the Pfeiffer organism isolated at autopsy from the lungs of influenza cases occurring during the epidemic. Morphologically the strains from the two diseases were almost identical. The cultures from the measles cases showed little tendency to develop bizarre forms even on heated blood-agar and then never in extreme degree. Davis* has reported the isolation of a strain of Pfeiffer bacillus possessing feeble hæmolytic properties. No hæmolysis was produced by our strains on human blood-agar or broth media made of 5 per cent of blood in meat infusion broth just acid to phenolphthalein (0.1 per cent normal acid). Only very scanty growth occurred in the unheated blood broth medium. Fairly abundant growth was secured in liquid media by partially laking the blood with two volumes of water. Preliminary observations were carried out on the spectroscopic changes occurring in cultures. Uninoculated control flasks of media showed typical absorption bands of oxyhæmoglobin. With whole blood slight growth occurred without any apparent change in the absorption bands. With laked blood after 48 hours the cultures showed bands characteristic of methæmoglobin; after 72 hours, in acidified samples a broad band also appeared in the green. Cultures from measles cases produced changes more readily than those obtained from the influenza patients, but these differences might readily be explained by a difference in the rate of growth.

The principal object of the comparison of the measles and influenza strains consisted in an attempt to find some fundamental biological differences between the organisms obtained from these two sources. Observations were conducted on the reactions of agglutination and complement fixation, on the resistance of the organisms to freezing and drying and on the effect of bile and of sodium hydroxide. A comparison was made of the local reaction of the two strains upon intracutaneous inoculation of rabbits; strains from measles cases were also inoculated into monkeys and into some human volunteers.

Immunity Reactions.—Both the agglutination test and the complement fixations failed to show any constant differences between the two strains of organisms; some of the measles strains reacted with the serum of measles and influenza convalescents and also with normal individuals. In some instances the serum of a measles convalescent fixed complement with strains of organisms obtained from either measles or influenza patients. No evidence was obtained which possessed any significance regarding the etiology or diagnosis of measles. In some experiments on phagocytosis, Pacchioni and Franchioni* re-

port that the serum of measles patients possesses a high opsonic index for Pfeiffer-like organisms.

For the agglutinations, a moderately heavy suspension of bacteria was prepared in physiological saline from a 48-hour growth on blood-agar. This suspension was mixed with an equal volume of serum in dilutions varying from 1-10 to 1-100. The mixtures were incubated at 37°C. for from 2 to 24 hours and at 55°C. for 12 hours. The majority of all the results were negative; only a comparatively few preparations showed well defined clumping.

The complement fixations were carried out with a sheep cell rabbit serum hæmolytic system, two units of complement being used. The antigen was prepared by digesting a saline suspension of the bacteria at 37°C. for 5 to 6 days. After centrifugalization, the opalescent supernatant fluid was titrated for its antigenic power; one-half of the maximum quantity permitting complete hæmolysis was employed in the tests. The serum to be tested was inactivated at 55°C. and 0.1 c. c. was employed; the total volume of the final preparation was 2 c. c. One series of antigens was prepared by alcoholic extraction of a saline suspension of bacteria that had been allowed to autolyse for one week at 37°C. Since these immunity reactions were essentially negative the results are not recorded in detail.

The results of the agglutination tests conducted by Wollstein¹² indicate that the Pfeiffer-like bacilli can be subdivided into smaller groups. Such evidence, unless very striking differences are obtained, does not constitute proof of distinct species. Accordingly, we did not carry the work on immunity reactions any farther. Some of the more general biological characteristics of these two strains of Pfeiffer organisms have been investigated in the search for evidence that might indicate the existence of distinct species in the hæmophilic group.

TABLE II

SHOWING EFFECT OF FREEZING ON PFEIFFER-LIKE ORGANISMS

Serial number	Growth on blood-agar after		
	5 freezings	10 freezings	15 freezings
STRAINS FROM MEASLES CASES			
2	Heavy	Heavy	Heavy
4	"	None
7	"	Slight	"
10	"	Heavy	Heavy
12	"	"	"
26	"	Slight	"
27	"	Heavy	"
28	"	"	"
STRAINS FROM INFLUENZA CASES			
A	Heavy	Slight	Heavy
B	"	"	None
C	"	Heavy	Heavy
D	"	Slight	None
E	"	Heavy
F	"	Heavy	None
G	"	None	"
H	"	Heavy	"

Effect of Freezing.—Many of the Pfeiffer cultures were found to be susceptible to even moderately low temperatures whereas others were resistant. The measles and the influenza strains did not fall into distinct groups. However, six of eight

cultures from measles cases in contrast to three of eight cultures from influenza patients were resistant to freezing.

Technique.—Emulsions of the Pfeiffer bacillus in physiological salt solution were rapidly frozen and thawed 15 times, a freezing mixture of ice and salt at about -10° to -12° C. being used. After each 5 freezings, cultures were made on human blood-agar plates. Table II gives a typical result.

Several repetitions of this experiment on these same cultures showed that the behavior of the individual strains was almost constant. Some of the strains were not only unable to withstand alternate freezing and thawing but were destroyed by continuous freezing at about -10° C. maintained for from two to three hours.

Effect of Drying.—These cultures of the Pfeiffer bacillus succumbed rather readily to drying for a short period. Under

TABLE III

SHOWING EFFECT OF DRYING ON PFEIFFER-LIKE ORGANISMS

Serial number	Growth on blood-agar	
	After 4 minutes	After 8 minutes
STRAINS FROM MEASLES CASES		
2	None	None
4	"	"
7	Alive	Alive
10	"	"
12	"	"
26	None	None
27	Alive	Alive
29	"	"
STRAINS FROM INFLUENZA CASES		
A	None
B	Alive	Alive
C	None	None
D	Alive	Alive
E	None	None
F	"
G	"	None

the conditions of the experiment, the measles strains survived a little longer than those from influenza patients but the differences were not marked.

Technique.—A coarse coil of platinum wire was dipped in a saline suspension of young cultures of the organism to be tested. The moistened coil of wire, free from any gross droplets of the emulsion, was suspended in a desiccator at room temperature for periods of 4, 8 and 12 minutes. Cultures were then made on blood-agar. A characteristic result is given in Table III, these results being constant on two repetitions except in the case of one culture (4) which was dead in one and alive in another of the two succeeding tests.

Action of Bile.—In contrast to their resistance to freezing and drying, the measles strains seemed more susceptible to the action of bile than the cultures obtained from influenza cases.

Technique.—Saline suspensions of 48-hour cultures of the Pfeiffer organisms were mixed with an equal volume of varying dilutions of bile. The mixture was incubated for 1 hour at 37°C. in a water-bath. Occasionally there was some macroscopic evidence of clearing, but in order to obtain definite results, cultures were made upon blood-agar. A similar technique was used in the later

experiments in which bile salt and sodium hydroxide were substituted for bile. The dilutions given in the tables represent the final strength after mixture with the bacterial emulsion.

The action of bile is illustrated in Table IV.

The difference in behavior of the two strains towards bile appears at first to be very striking; moreover, the individual

in general were the reverse of those obtained with bile. The following data in Table V are characteristic.

From Table V it will be seen that there is only a small range of dilutions within which it is possible to demonstrate differences with sodium hydroxide; moreover, with some strains of organisms it is very difficult to obtain constant results under apparently identical conditions.

Action of Bile Salts.—Whole bile contains not only the biliary salts but an appreciable amount of alkali; since bile and the hydroxide act in a somewhat different manner on these Pfeiffer strains, it seemed desirable to try the action of bile salts alone. As in the case of other manifestations of the action of bile, the effect of the purified salt was less striking than the action of the whole product. Sodium taurocholate in $2\frac{1}{2}$ per cent concentration killed all cultures tested; at 1 per cent the majority of the cultures were killed, whereas with one-half per cent about half of the measles and also half of the influenza strains were killed; at one-tenth per cent, all but 3 of 16 strains lived. Certain strains of the Pfeiffer bacillus are therefore approximately as susceptible as the pneumococcus to the purified bile salt.

Effects of Inoculation.—These cultures exhibited very little virulence upon inoculation into the smaller laboratory animals. Four cultures of measles strains and three of the influenza strains were tested upon rabbits, guinea-pigs, and mice by intraperitoneal inoculation. The rabbits and guinea-pigs showed no symptoms; occasionally the mice were killed in from two to three days by the injection of the growth from one to two blood-agar slants. A series of rabbits was inoculated intracutaneously with the two strains of organisms. Seven cultures from measles patients were tested; in all cases well marked oedema and inflammation developed during the first 24 hours, these symptoms persisting for from two to four days. Of seven cultures from influenza cases, tested in a similar manner, five showed virtually no reaction and two behaved precisely like the cultures from measles cases. The influenza cultures had been isolated approximately two months earlier than those obtained from measles patients; the two influenza strains producing inflammation were obtained earlier in the epidemic than the five causing little or no reaction.

Two adult monkeys (*Macacus rhesus*) were inoculated with a mixture of eight strains obtained from the sputum and conjunctivæ of measles cases. These cultures had been isolated for periods varying from one to three weeks. The growth from 48-hour cultures on blood-agar plates was suspended in salt solution. This emulsion was thoroughly rubbed over the mucous membranes of the eyes, nose, mouth and throat. In one monkey the mucous membrane of the mouth was scarified slightly on the right side; on the left side 0.5 c.c. of the bacterial suspension was injected under the mucous membrane. The scarified mucous membrane healed promptly and no local lesion developed at the site of the inoculation under the mucous membrane. Each of these animals also received intraperitoneally 2 c.c. of a moderately heavy saline suspension of these cultures.

TABLE IV

SHOWING GROWTH ON BLOOD-AGAR AFTER EXPOSURE TO BILE

Serial number	Final dilution of bile			
	1:5	1:10	1:20	1:40
STRAINS FROM MEASLES CASES				
1	None	None	None	Slight
2	"	"	Slight	"
4	"	"	"	Heavy
7	"	"	"	"
10	"	"	"	"
12	"	"	None	Slight
26	"	"	Slight	Heavy
27	"	"	"	"
29	"	"	"	Slight
STRAINS FROM INFLUENZA CASES				
B	Heavy	Slight	Heavy	Heavy
C	"	Heavy	"	"
D	Slight	Slight	Slight	Slight
E	None	None	None	None
F	Heavy	Heavy	Heavy	Heavy
G	"	Slight	Slight	"
H	Slight	Heavy	Heavy	"

cultures in four repetitions of this test behaved constantly in this manner. However, the total number of cultures tested is small and even in moderate dilutions of 1:40 the difference disappears altogether.

Action of Sodium Hydroxide.—The effect of sodium hydroxide upon the cultures was rather variable, but the results

TABLE V

SHOWING GROWTH ON BLOOD-AGAR AFTER EXPOSURE TO SODIUM HYDROXIDE

Serial number	Final dilution of sodium hydroxide				
	N/5	N/10	N/20	N/40	N/100
STRAINS FROM MEASLES CASES					
1	None	None	Slight	Heavy	Heavy
2	"	"	"	Slight	Slight
4	"	None	"	Heavy	Heavy
7	"	"	"	"	"
10	"	"	"	"	"
12	"	"	"	Slight	Slight
26	"	"	None	None	"
27	"	"	Slight	Heavy	Heavy
29	"	"	None	"	"
STRAINS FROM INFLUENZA CASES					
B	None	None	None	Slight	Heavy
C	"	"	"	None	Slight
D	"	"	"	Slight	Heavy
E	"	"	"	"	Slight
F	"	"	"	None	"
G	"	"	Slight	Heavy	Heavy
H	"	"	None	Slight	Slight

Daily temperatures and white counts were made upon both monkeys. One remained entirely normal; the other, after an incubation period of six days developed definite malaise as evidenced by the loss of strength and loss of appetite. This animal had been under close observation for four months prior to these injections and had remained entirely free from any symptoms. During the period of malaise a suggestive drop occurred in the leucocyte count, unaccompanied, however, by any febrile reaction. The symptoms disappeared before the normal white count was fully re-established. At frequent intervals after inoculation, cultures were made from the mucous membranes on blood-agar. Pfeiffer-like organisms were not recovered from either monkey. The temperature and counts in the monkey which became ill were as follows:

INOCULATION OF MONKEY WITH PFEIFFER-LIKE STRAINS OF ORGANISMS

Days after inoculation	Temperature	White count	Room temperature
..	101.8	13,750	66°
1	100.8	25,250	63.5°
2	101.6	13,600	67°
3	100.2	23,800	77°
4	101.4	15,300	78.8°
5	100.4 ¹	14,600	66°
6	101.2 ¹	10,000	68°
7	101.0 ²	10,800	68°
8	101.6 ³	10,600	68°
9	101.2 ⁴	15,500	68.9°
10	102.6 ⁴	9,700	66°
11	102.0	11,100	68.9°
12	101.8	15,400	68°
13	101.6	16,000	68°
14	103.2	13,300	68.9°
15	102.5	15,300	68.9°
16	101.6	16,200	68.9°
17	102.0	17,300	68°
18	101.2	15,700	67°
19	100.6	16,400	68.9°
20	100.4	17,400	66°

¹ Cyanosis, conjunctivitis and loss of appetite.

² Deep cyanosis, critically ill.

³ Marked improvement, eyes clearing, appetite good.

⁴ Apparently normal.

A few inoculations of human volunteers were undertaken with the Pfeiffer strains obtained from measles cases. A mixture of five strains was employed, three of which were obtained from the sputum and two from the conjunctivæ. These cultures had been under artificial cultivation approximately six to eight weeks. All were easily killed by bile and all were resistant to freezing.

For the protection of the individual, the precautionary measures were taken, which have already been outlined for the inoculation of volunteers with the virus of measles;* these precautions include observations for the exclusion of the Pfeiffer bacillus. As an additional safe-guard for the first inoculation, an individual was chosen who was immune to measles and who had had influenza in the recent epidemic. The mucous membrane of the eyes, nose and throat was inoculated with a saline emulsion of the five strains. During the next two weeks cultures were made at three-day intervals on blood-agar and mice were inoculated with sputum for the re-

covery of the Pfeiffer organism. The cultures were negative and the individual himself developed no symptoms.

Accordingly, a volunteer was inoculated who had had influenza recently but not measles. No symptoms appeared and the cultures failed to colonize. Two additional volunteers were inoculated, who as far as could be determined, had had neither measles nor influenza. Both of these subjects remained entirely free from symptoms; the white blood count and the temperature did not vary beyond the normal limits, and the cultural examinations failed to show any evidence of colonization of the inoculated organisms. Under natural conditions, the Pfeiffer bacillus can readily establish itself in the mucous membranes. Hence the failure to produce symptoms would have possessed much more significance if successful colonization of the inoculated cultures had been obtained. These negative results are of some interest in view of the discussion regarding the occurrence of *B. influenza* in normal throats; in some instances, at least, it does not persist when heavily inoculated into healthy individuals.

Davis⁵ found the Pfeiffer organism in a high percentage of cases of pertussis. Under the more favorable circumstances of an interepidemic period, this investigator reports the production of respiratory symptoms with prolonged colonization of the bacillus in man.

DISCUSSION

A comparison of different strains of the Pfeiffer bacillus showed considerable variation, more especially as regards their resistance to freezing and to the destructive action of bile. The attempt to separate the cultures into two distinct groups becomes very difficult during an epidemic on account of the opportunity for mixed and for cross infection. It is to be expected, for example, that a group of cultures obtained from measles cases would contain some strains behaving like the majority of those obtained from influenza. Such variations were numerous, but the individual strains were not consistent in the series of tests that were employed. Thus, two of the measles strains were susceptible to freezing. In this respect they behaved like the influenza cultures; yet these same strains were resistant to drying and susceptible to the action of bile, conforming in these tests to the majority of the other cultures from measles. The complete record of these strains that were tested is shown in the following outline.

VARIATIONS IN PFEIFFER-LIKE ORGANISMS

Tests employed	Freezing	Drying	Bile 1-10	NaOH N/20	Intracutaneous inoculations
Serial number of measles strains resembling influenza cultures	4 7	2 4 26	None	26 29	17 29
Serial letter of influenza strains resembling measles cultures	A C E	B D	E	G	B I

Our information concerning the Pfeiffer bacillus is as yet extremely meagre; satisfactory methods have not yet been

* Bull. Johns Hopkins Hosp., 1919, XXX, 257.

devised for performing tests for pathogenicity or for fermentation and immunity reactions. At present this bacillus is identified by its size, the lack of motility, its decolorization by Gram's stain and its multiplication only in the presence of hemoglobin.* The situation may be illustrated by comparison with the very broad typhoid-colon group of organisms. As regards *B. coli* and *B. typhosus* these organisms are virtually identical in their size, motility and staining characteristics. Without either fermentation tests or immunity reactions it would become a difficult problem to separate them into perfectly distinct species or even to determine the etiology of typhoid fever.

In the absence of definite information it seems unwise to attempt any final statements concerning *B. influenzae* and its possible etiologic rôle in the respiratory diseases in which it is most commonly found. Certainly the general opinion at present is decidedly against the acceptance of the bacillus as the specific etiologic agent of influenza. This opinion is held largely because of the frequent failure to find the organism in typical cases and because of its common occurrence in other respiratory diseases. As in pneumonia it is conceivable that various organisms might give rise to more or less definite symptoms of influenza; the Pfeiffer-like bacilli, moreover, are not more widely distributed in healthy individuals than is the pneumococcus. Some consider that *B. influenzae* is purely a secondary invader in a variety of diseases initiated by other agents; when the bacillus is found in pure culture in lesions of the lungs, the natural explanation of a primary etiologic action is set aside and a hypothetical virus is postulated. However, there is good reason to believe that serious symptoms may result when an infection with the Pfeiffer bacillus has become established; its acceptance as a specific etiologic agent, however, seems to us to be contingent upon some division of these organisms such as the recognition of distinct species or of virulent and avirulent varieties.

SUMMARY

1. The examination of a group of measles cases occurring a few weeks after an epidemic of influenza showed the presence of an organism indistinguishable from the Pfeiffer bacillus in 25 of 31 cases.

* Neisser reports that the Pfeiffer bacillus can be cultivated indefinitely on plain agar in "symbiosis" with ordinary micrococci.

2. This organism was obtained readily from the sputum and with little difficulty from the conjunctivæ. A highly parasitic, hemoglobin-requiring organism was obtained in one of two cases from an excised inguinal gland. The Pfeiffer organism was not obtained from the blood stream nor from the excised skin lesions.

3. With the subsidence of the active symptoms of measles these micro-organisms disappeared rather rapidly in about three-fourths of the cases.

4. Cultures of the Pfeiffer organism from cases of measles failed to colonize when inoculated on the mucous membrane of four healthy volunteers; two of these individuals supposedly had not had either measles or influenza.

5. A comparison was made of the strains of the Pfeiffer bacillus isolated from measles and from influenza. The results showed considerable variation in the behavior of the individual strains. It is theoretically possible that the hemoglobin requiring bacilli represent a group of micro-organisms containing distinct species.

6. The occurrence of the Pfeiffer bacillus both in measles and in influenza constitutes suggestive evidence against its etiologic relationship in either disease. This evidence would be materially strengthened provided the identity of the strains from these two sources were accurately established.

7. The evidence which is available at present is not sufficiently complete to exclude the specific etiologic rôle of the Pfeiffer bacillus in some of the acute respiratory diseases.

LITERATURE

1. Paltauf, R.: Wien. klin. Wchnschr., 1899, XII, 576.
2. Giarre, C., and Picchi, L.: Clin. mod., 1900, VI, 178. Sperimentale. Arch. di biol., 1903, LVII, 475.
3. Albrecht, H., and Ghon, A.: Ztschr. f. Heilk., Abt. f. patholog. Anat., 1901, XXII, 29.
4. Jehle, L.: Ztschr. f. Heilk., Abt. f. Int. Med., 1901, XXII, 190.
5. Süsswein, J.: Wien. klin. Wchnschr., 1901, XIV, 1149.
6. Liebscher, C.: Prag. med. Wchnschr., 1903, XXVIII, 85.
7. Klienberger, C.: Deutsche med. Wchnschr., 1905, XXXI, 575.
8. Davis, D. J.: Jour. Infect. Dis., 1906, III, 1.
9. Pacchioni, D., and Franchioni, C.: Jahrb. f. Kinderh. u. physische Erzieh., 1908, LXVIII, 39.
10. Reiss, E., and Gins, H. A.: Münch. med. Wchnschr., 1911, LVIII, 2211.
11. Woolley, P. G.: Jour. Labty. and Clin. Med., 1919, IV, 330.
12. Wollstein, M.: Jour. Exper. Med., 1905, VII, 335.
13. Neisser, M.: Deutsche med. Wchnschr., 1903, XXIX, 462.

JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXX is in progress. The subscription price is \$4.00 per year.

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THE REACTION OF THE LEUCOCYTES IN EPIDEMIC INFLUENZA

By BEVERLY DOUGLAS

During the epidemic of influenza occurring in the fall of 1918, the presence of a leucopenia in practically all the cases was commented on by numerous observers. An opportunity was afforded during the course of the epidemic in The Johns Hopkins Hospital to make rather extensive and careful studies of the blood, which it seems worth while to put on record. The data can best be presented in the form of tables, with notes appended thereto.

1. *General Course of the Leucocyte Curve in Uncomplicated Epidemic Influenza.*—It seemed that information of most value about the general course of the leucocyte curve could be obtained by compiling the averages of counts made in a number of cases on various days. The results of such compilations are recorded in Table I and graphically represented in Chart 1. The following points may be commented on:

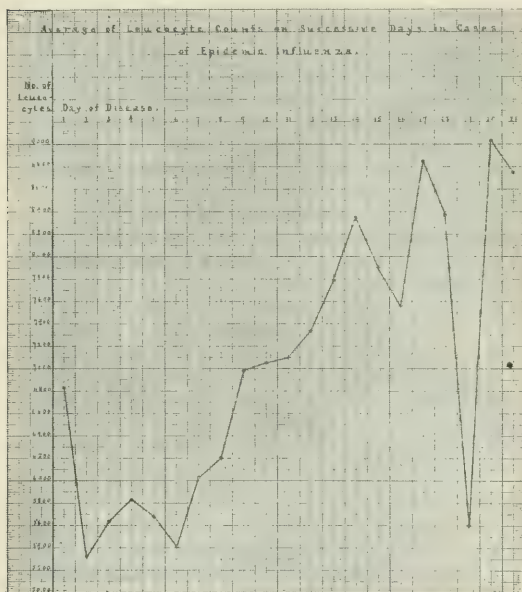


CHART 1.

Leucopenia is present, even on the day of onset of symptoms, the count falling somewhat on the following day and then gradually rising. One might almost imagine that there is some initial shock which depresses the leucocytes and from which they gradually escape during the subsequent days of the disease. It is also noteworthy that the return to normal count comes gradually, the average count still being subnormal on the twenty-first day.

Table I also shows the reaction of the leucocytes in the cases of influenza complicated by bronchopneumonia. These

counts bear out the impression obtained at the time of the epidemic that a complicating bronchopneumonia, as a rule, does not lead to leucocytosis. An attempt was made to see if

TABLE I.—AVERAGE LEUCOCYTE COUNTS COMPILED FROM HISTORIES OF 250 EPIDEMIC INFLUENZA AND SUSPECTED INFLUENZA PATIENTS

EPIDEMIC OF OCT.-NOV., 1918. J. H. H.

	Flu	Acute resp. not flu	Afebrile flu	Flu & bronchopneu. fatal	Flu & bronchopneu. not fatal	Flu & bronchopneu. not fatal
3 or more days before onset.				3	7	4
2 days before onset.				3127	3430	3656
Day before onset.				1	5	4
Day of onset....	25 ¹	4	1	2625	4580	4813
2d	6833	13120	5800	2	5	3
3d	48	7	°	4705	4010	3880
4th	5323	8130	°	6 ²	16 ²	10 ²
5th	41	5	2	4250	4204	4175
6th	5644	7054	6700	5440	5403	5396
7th	33	°	1	4	15	11
8th	5838	°	5760	6260	5564	5305
9th	18	1	°	2	10	8
10th	5681	8800	°	3280	5850	6492
11th	31	1	°	3	11	8
12th	5412	8000	5200	8550	8644	8677
13th	13	1	1			7
14th	6036	4850	9450			7530
15th	28	7	3			8
16th	6203	8450	6910			8860
17th	14					4
18th	6985					13960
19th	21					5
20th	7050					9740
21st	17					5
22 days or more..	7100					8432
Grand average ...	25					4
	7340					7810
	25					4
	7790					10860
	25					2
	8350					9340
	23					1
	7900					9800
	12					4
	7560					7630
	15					1
	8850					8120
	7					
	8370					
	2					
	5600					
	6					
	9030					
	5					
	8752					
	2					
	5230					
	436					
	6673					
				25	126	174 ³
				5040	6745	7066

¹ Index number = number of counts averaged for that day.

² Onset of pneumonia.

³ All except uncomplicated flu.

the severity of the case from the clinical standpoint could be correlated with the extent of the leucopenia. For this purpose the cases were divided into mild, moderate and severe.

Counts made on or before the fourth day after onset showed in the mild cases an average of 5500, in the moderate, an average of 5800, and in the severe, an average of 5400. The lowest single count observed—one of 1900 cells, was in an extremely mild case. It seems, therefore, that in a general way, the extent of the leucopenia does not vary with the severity of the disease.

TABLE II.—SUPPLEMENTARY TABLE SHOWING HIGHEST AND LOWEST COUNTS ON EACH DAY. (See No. 1)

INFLUENZA EPIDEMIC OCT.-NOV., 1918. J. H. H.

	Fry	Acute resp. out 50	Acute in	Incubation pneum. 1000	Fry To 1000 1000
3 or more days before onset				Too Few.	4960
2 days before onset					2640
Day before onset					2625
Day of onset	10700	22480			3800
2d	3440	6000			4760
3d	10440	9200			4650
4th	2500	7000			3240
5th	11720	10000			6400
6th	2640	4800			3400
7th	12000	8800			2675
8th	2240	8800			13000
9th	12500	8800			2460
10th	10600	8000			14600
11th	3000	8000			13100
12th	10200	4850			2600
13th	2400	4850			3320
14th	10100	11980			18400
15th	2120	5440			3240
16th	11500				2200
17th	3260				2360
18th	12060				11900
19th	2640				4650
20th	12640				14480
21st	4720				5760
22nd	14600				24720
23rd	3100				8160
24th	10600				11920
25th	5200				6120
26th	19000				10200
27th	2500				6300
28th	13440				9800
29th	4000				3640
30th	10600				13120
31st	3220				8640
32nd	20800				10280
33rd	4480				8400
34th	14600				9800
35th	6250				9800
36th	7000				8750
37th	4040				5080
38th	14600				8120
39th	5080				8120
40th	12500				
41st	7100				

2. In Table II, which should be studied in connection with Table I, are presented the highest and lowest individual counts encountered in the various cases of leukocytosis. From this table, it is apparent that despite the general tendency to a leucopenia, there may in some cases be a moderate leucocytosis.

TABLE III.—AVERAGES OF PER CENT PMN. AND TOTAL
LEUCOCYTE COUNTS COMPILED FROM 250
INFLUENZA HISTORIES IN J. H. H.

EPIDEMIC OF OCT.-NOV., 1918

Day of Disease	Av. Wts.	Av. P.M.N.	Day of Disease	Av. WBC.	Av. P.M.N.
Onset	4 ¹ 5220	72%	11th	3 6387	45%
2d	13 5575	66%	12th	6 7843	60%
3d	6 7900	59%	13th	3 8870	57%
4th	9 5675	53%	14th	6 7930	61%
5th	2 7350	61%	15th	11 7450	62%
6th			16th	3 6550	69%
7th	1 6600	62%	17th	4 8330	62%
8th	3 6330	60%	18th	1 7400	79%
9th	5 6456	56%	19th	11 8080	73%
10th	4 9950	66%	20th	2 9870	47%

¹ Small text number within or at end of average.

TABLE IV.—INFLUENZA. VARIATION OF PERCENTAGE OF PMN. CELLS C. W. B. COUNTS (COUNTS AND DIFFERENTIALS ON SAME DAYS)

EPIDEMIC OF OCT.-NOV., 1918. J. H. H.

[illegible]

3. Table III attempts to correlate the polymorphonuclear leucocytes with the total count. In this relatively small number of cases, no significant relationship is made out.

4. Table IV shows the relationship of the polymorphonuclears to the total count from another point of view—namely, the total count rather than the day of the disease.

Conclusions.—From these tabulations, the following general conclusions may be drawn:

Leucopenia is the rule in epidemic influenza, although a few cases may show normal counts or a slight leucocytosis.

The leucopenia frequently is present on the first day of the disease, after which it may become more marked for a few days, with a subsequent gradual tendency to rise until the

normal mark is reached. In some cases the normal mark is overshoot during convalescence, and leucocytosis may be present.

There is no constant relation between the leucocyte count and the severity of the disease.

The persistence of the leucopenia is the rule, even where bronchopneumonia, fatal or non-fatal, supervenes.

Differential counts show an absolute relative decrease in polymorphonuclear cells, as well as during the stage of leucopenia, varying to some extent with the total count.

Acute non-influenzal respiratory infections, as a rule, are accompanied by a leucocytosis.

A leucopenia is, therefore, a reliable diagnostic sign in epidemic influenza.

BOOKS RECEIVED

American Pediatric Society. Transactions of the American Pediatric Society. Thirtieth Session. Held at the Curtis Hotel, Lenox, Mass., May 27, 28, and 29, 1918. Edited by Oscar M. Schloss, M. D. 1918. 8°. 331 pages.

The Control of Hookworm Disease by the Intensive Method. By H. H. Howard, M. D. Publication No. 8. 1919. 8°. 189 pages. The Rockefeller Foundation International Health Board, New York City.

Manual of Neuro-Surgery. Authorized by the Secretary of War under Supervision of the Surgeon-General. Prepared under the direction of the Neuro-Surgical Section of the Division of Surgery, in collaboration with the Sections of Head Surgery, General Surgery, Orthopedic Surgery, and Neuro-Psychiatry, the Army Neuro-Surgical Laboratories, and the Instruction Laboratory of the Army Medical Museum. 1919. 8°. 492 pages. Government Printing Office, Washington.

A Text-Book of Urology in Men, Women and Children. Including Urinary and Sexual Infections, Urethroscopy and Cystoscopy. By Victor Cox Pedersen, A. M., M. D., F. A. C. S. Illustrated with 362 engravings, of which 152 are original, and 13 colored plates. 1919. 8°. 991 pages. Lea & Febiger, Philadelphia and New York.

Pulmonary Tuberculosis. By Maurice Fishberg, M. D. Second edition, revised and enlarged. Illustrated with 100 engravings and 25 plates. 1919. 8°. 744 pages. Lea & Febiger, Philadelphia and New York.

Roentgen Interpretation. A Manual for Students and Practitioners. By George W. Holmes, M. D., and Howard E. Ruggles, M. D. Illustrated with 181 engravings. 1919. 8°. 211 pages. Lea & Febiger, Philadelphia and New York.

The Principles of Nursing. By Charlotte A. Brown, R. N. Illustrated. 1919. 12°. 262 pages. Lea & Febiger, Philadelphia and New York.

Pneumotorax Artificial, y Otras Intervenciones en la Tuberculosis Pulmonar. Estudio Critico y Clinico. Por el Doctor Juan B. Morelli. 2 volumes. 1918-1919. 8°. 1246 pages. Imprenta Nacional, Montevideo.

Medical Report of the Durand Hospital of the John McCormick Institute for Infectious Diseases. For the First Five Years, March 12, 1913 to March 12, 1918. George H. Weaver, M. D., Physician-in-Charge. 1919. 4°. 32 pages. Chicago.

PUBLICATIONS

The following eight monographs:

Free Thrombi and Ball-Thrombi in the Heart. By J. H. HEWITT, M. D. 82 pages. Price, \$1.00.

Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, \$1.00.

Primary Carcinoma of the Liver. By M. C. WINTERNITZ, M. D. 42 pages. Price 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, \$2.00.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, \$2.00.

Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SLADEN, M. D., and MILTON C. WINTERNITZ, M. D. Price, 75 cents.

Leukaemia of the Fowl: Spontaneous and Experimental. By HARRY C. SCHMEISSER, M. D. Price, \$2.00.

The Structure of the Normal Fibers of Purkinje in the Adult Human Heart and Their Pathological Alteration in Syphilitic Myocarditis. By O. VAN DER STRICH and T. WINGATE TODD. Price, \$2.00.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time

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HENRY MILLS HURD

THE FIRST SUPERINTENDENT OF THE JOHNS HOPKINS HOSPITAL

By THOMAS S. CULLEN *

The subject of this sketch, probably the best known hospital superintendent in the United States, an expert on hospital organization and management, professor of psychiatry, author and editor, was a product of Michigan, a state that has furnished many well-known figures in American medicine.

Shortly after Dr. Hurd came to Baltimore a charming sketch of his early life and of his manifold activities in Kalamazoo and Pontiac appeared from the pen of Dr. C. B. Burr, his successor at the Eastern Michigan Asylum at Pontiac. This tribute appeared in the *American Journal of Insanity*,

1899, Vol. 46, p. 303. As it cannot be improved upon I shall give it in detail:

Henry M. Hurd, A. M., M. D., the recently appointed director of The Johns Hopkins Hospital, Baltimore, and the subject of our photogravure, was born May 3, 1843, at Union City, Branch Co., Michigan. His parents, Theodore C. and Ellen E. (Hammond) Hurd, were of New England (Connecticut) stock. His father, a pioneer physician, came to Michigan in 1834; and, worn out by laborious practice amid the hardships and privations of pioneer life in a malarious country, died at the early age of 39, leaving a wife and three little boys.

His mother remarried in 1848, and in 1854 the family removed to Galesburg, Ill. In 1858 he entered Knox College, where he spent two years. Subsequently he devoted a year to teaching and general study, and in 1861 entered the junior class of the University of Michigan. He graduated from the university in 1863, and in the same year began the study of medicine with his stepfather, who was also a physician. He attended lectures at the Rush Medical College, Chicago, and at the University of Michigan, and graduated from the department of medicine and surgery of the university in 1866. The year following graduation he spent in New York in study and hospital work. Subsequently he removed to Chicago, where he engaged in dispensary and general practice for two years. It was during the time of his residence in Chicago, in 1870, that he received the appointment of assistant physician to the Michigan Asylum for the Insane at Kalamazoo, and entered that field of medical practice in which he has achieved so much distinction. He served the asylum in the capacity of assistant physician for eight years, at the end of which time he became assistant superintendent. On the opening of the Eastern Michigan Asylum at Pontiac in the fall of the same year he was appointed its first superintendent, and occupied this position continuously for 11 years. Possessing rare skill as an organizer, broad culture, literary attainments of a high order, a thorough medical

* I have written this article at the request of Judge Henry D. Harlan, president of the Board of Trustees of the hospital, and of Mr. George K. McGaw, one of the trustees of the hospital—one of Dr. Hurd's warmest friends and the donor of a large sum of money towards the erection of the Henry M. Hurd Library Building which is to be on the hospital grounds.

It was my good fortune to come to the hospital in 1891, just two years after it opened. In my early years I viewed Dr. Hurd's work from the immature standpoint of the junior intern, later as a senior house officer, and for at least 15 years Dr. Hurd has been one of my very best friends.

It has been a delight to browse through his early writings, to digest the chief events of the hospital as they were sketched by him in the yearly reports, and to epitomize the results of his labors since he retired from the active management of the hospital in 1911. I had always looked upon Dr. Hurd as an indefatigable worker, but until now I have never had the slightest conception of the tremendous amount he has accomplished and of how largely he has been responsible for the phenomenal success of The Johns Hopkins Hospital.

training and a long asylum and hospital experience, he brought to the work of organizing the Eastern Michigan Asylum those qualities which enabled him to place it at once among the progressive asylums of the country. He early identified himself with the Association of Medical Superintendents, and was an earnest, faithful and zealous member of this body.

During the period of his administration of affairs of the Eastern Michigan Asylum he has seen the treatment of the insane revolutionized. For the abolition of restraint, the employment of the insane, the extension of the system of night-nursing, the development of the "cottage plan," and the introduction of home comforts into the dull, unattractive institutional life of previous years, he has been an ardent and enthusiastic advocate. To him, perhaps, as much as to any other man among the present generation of alienists in this country is due the rapid growth of progressive methods in the care of the insane, and the advanced position which American psychiatry is taking. His mental culture, which enabled him to grasp intricate problems in all their details, his philanthropic instincts, his ready sympathies and his keen insight into the needs of the insane, conjoined with the quick perception of the skilled physician, made him an ideal asylum superintendent. His personal presence was inspiring; he infused his own spirit of tireless energy among his subordinates, he unified his staff and his corps of employés, and could always rely upon their thorough coöperation. In 1881 he visited Europe for travel and investigation in the special lines of work in which he was engaged. The results of this trip were the subject of a special communication to the joint Boards of Trustees of the Michigan asylums, and were published in connection with the biennial report of the Eastern Michigan Asylum for 1882. His writings upon the subject of mental medicine have been voluminous and of a high order. Aside from the numerous papers published in the *American Journal of Insanity*, as reference to its files for the past 11 years will show, many of great merit have appeared elsewhere.

Among his recent and most scholarly productions is his presidential address in 1889 before the alumni association of the medical department of the University of Michigan, on "The Mental Hygiene of Physicians." His reports of the Eastern Michigan Asylum are written in a masterly and finished style, and have been warmly received and favorably noticed by the profession of this and foreign countries. He was a vice-president of the Ninth International Medical Congress, is a member of the Michigan State Medical Society and of the Detroit Academy of Medicine, and is corresponding member of the Detroit Medical and Library Association.

In June of the present year there came to him, without previous intimation, the tender of the position of director of The Johns Hopkins Hospital. The offer came as a gratifying surprise, but he hesitated to accept it. He was reluctant to relinquish the work to which he had devoted his best years, to separate himself from his patients—may of whom had long been objects of his care and solicitude—and from friends endeared to him by the strongest ties. He hesitated to abandon the work in which he had been so long and successfully engaged, and in which the prospects for future usefulness opened wide and ever wider before him; but considerations, paramount among which were the increased opportunities for the education of his children, constrained him to accept the position.

By mental endowments and education he is peculiarly well fitted for the responsible and delicate duties of a hospital director. He is thoroughly deserving of his recent very great honor, and will adorn the position to which he has been called; but as we write these lines, the feeling returns with ever-increasing force, that in the gain of The Johns Hopkins Hospital, the profession of

psychiatry sustains an irreparable loss, and the asylum system of Michigan is deprived of its most illustrious exponent.

When Dr. Hurd came to Baltimore to see The Johns Hopkins Hospital and to meet the trustees of the hospital one of the trustees from the Eastern Michigan Asylum at Pontiac came with him with the intention of urging his superintendent to decline the call. After he had met the trustees and had visited the hospital he turned to Dr. Hurd and said: "My object in coming with you was to see that you returned to Michigan, but I have changed my mind. If they offer you this position and you do not accept it, you will make the mistake of your life."

PAPERS ON PSYCHIATRY PUBLISHED BY DR. HURD PRIOR TO HIS COMING TO BALTIMORE

Amid his many asylum duties Dr. Hurd found time to do much writing and, as intimated by Dr. Burr, contributed a great deal to our knowledge of insanity. In 1880 he published a paper on "Recent Judicial Decisions in Michigan Relative to Insanity." This was followed in 1881 by "A Plea for Systematic Therapeutical, Clinical and Statistical Study." In this paper Dr. Hurd carefully analyzed the methods employed in the various asylums and clearly pointed out where improvements might with much profit be inaugurated. On page 11 he says:

Much of the present statistical information contained in the published reports of the institutions for the insane is unsatisfactory. There are tables enough, but they lack uniformity, precision in statement and practical utility.

Their lack of uniformity is well illustrated by the varying number of tables given in different reports, taken at random from a package before me.

In concluding this article Dr. Hurd says:

In this earnest plea for more systematic therapeutical, clinical and statistical inquiries, I would not be understood as criticizing the thorough work now done in connection with asylums. I have merely attempted to point out the necessity for further progress, and have suggested methods which would tend to increase the efficiency of asylum work.

In 1882 Dr. Hurd published papers on "Practical Suggestions Relative to the Treatment of Insanity" and "The Treatment of Periodic Insanity."

At a sanitary convention held in Pontiac in January, 1883, Dr. Hurd gave a most interesting address on "The Hereditary Influence of Alcoholic Indulgence Upon the Production of Insanity." His views as expressed 36 years ago tally so well with our present conception of this most important subject that I quote his conclusions:

In the foregoing paper I have endeavored to show that inebriety in parents is a frequent cause of insanity in their children, because drunkenness produces a transient insanity, even in a healthy brain; chronic drunkenness produces organic brain diseases, bringing in their train impairment of the memory, inactivity of the reason, a weakening of the will, and a loss of the natural affections; also moral perversions and vicious propensities, and finally, unmistakable diseases of the mind and nervous system—all of which are capable of transmission to children.



Theodore, aged 9
Charles, " 4
Henry, " 6
Galesburg, Ill.



Theodore, aged 13
Henry, " 10
Charles, " 8
Taken about 1853.
Galesburg, Ill.



Henry M. Hurd
in 1863, aged 20.
Ann Arbor, Mich.



Henry M. Hurd
in 1868, aged 25.
Galesburg, Ill.



Theodore Hurd,
and Henry M. Hurd
aged 27, April, 1870.
Galesburg, Ill.



Henry M. Hurd,
aged 31, in 1874
Chicago, Ill.

THE EVOLUTION OF HENRY M. HURD

These pictures were carefully treasured by Dr. Hurd's mother. They were obtained surreptitiously and no one will be more surprised to see them here than Dr. Hurd himself.

That the children of inebriate parents inherit diseases, such as epilepsy, hysteria, chorea and idiocy, or if not actual diseases, nervous systems which are abnormally responsive to every form of disturbing influence and are easily disordered.

That between the ages of 20 and 45 insanity is liable to be developed in the children of inebriates, and that insanity of this type is recovered from imperfectly or not at all.

And finally, that however much people may differ as to the expediency of "prohibition," so-called, in the present state of public sentiment, there should be no difference of opinion among thinking men as to the right and duty of the state to take strenuous measures to prevent the transmission of an inebriate heredity to children.

During 1883 Dr. Hurd also published a paper entitled "Future Provisions for the Insane in Michigan." In this article he sketched in a most interesting way the haphazard manner in which insane patients were looked after in Michigan until the opening of the asylum for the insane at Kalamazoo. He spoke in no uncertain terms of the duty of the state to care for the insane within her borders. The concluding paragraph in this article reveals very clearly the wise statesmanship of Dr. Hurd:

I would reiterate the conviction that it is the duty of the state to continue to care for her insane in the state asylums: that no consideration of false economy should prevent her from doing everything which can be done for the comfort and restoration of every insane person. If he requires the restraint and seclusion of an asylum for the dangerous insane, he should have it. If he requires curative treatment in a hospital, or suffers from a form of disease which calls for constant nursing, he should have that. If his welfare will be promoted by giving him labor, the liberty of home, and a manner of life nearly resembling that of a private family, he should receive them. No money should be wasted upon buildings, surroundings, or care. Sufficient, however, should be expended to render each unfortunate as comfortable as his condition will permit. Anything less than this is unworthy a great state like Michigan.

Dr. Hurd in 1883 also published "The Minor Treatment of Insane Patients." In 1886 he published an interesting article on "Paranoia." During the year 1886 we find two articles from his pen "The Relation of General Paresis and Syphilitic Insanity" and "The Data of Recovery from Insanity." In 1887 "Gastric, Secretory and Other Crises in General Paresis" and "The Colony System of Michigan" appeared. In 1888 Dr. Hurd published an important article on "The Religious Delusions of the Insane," also an article on "Imbecility with Insanity." In 1889 he also contributed a paper entitled "A Case of Inebriety with Insanity; with Remarks."

DR. HURD, THE FIRST SUPERINTENDENT OF THE JOHNS HOPKINS HOSPITAL

Dr. Hurd was appointed superintendent of The Johns Hopkins Hospital in June, 1889, and assumed the duties of the position on August 1, at which time President Gilman, who had acted as director of the hospital since the preceding February, and Dr. John S. Billings, who had been medical advisor to the Board of Trustees for 12 years, terminated their connection with the hospital. Dr. Hurd, as has already been mentioned, was the first superintendent of the Eastern Michi-

gan Asylum at Pontiac. Here he had taken charge of a brand new institution, had worked out the details of its management and had piloted its destiny most successfully for 11 years. Here at the Hopkins he had a similar opportunity, differing only in that the patients were suffering from bodily instead of mental ills. In this institution he was destined to establish later the most harmonious relationship between the hospital and The Johns Hopkins Medical School which opened its doors in 1893. His wise council, his broad vista and his tact have in large measure been responsible for the continuous cordial and intimate relations that have always existed between the medical school and the hospital.

Dr. Burr in his tribute to Dr. Hurd said, "His reports of the Eastern Michigan Asylum are written in a masterly and finished style, and have been warmly received and favorably noticed by the profession of this and foreign countries." The same standard of excellence shown in the Michigan reports has been maintained in the annual reports of The Johns Hopkins Hospital. In fact, when the history of this institution is written it will only be necessary to amplify what has already been succinctly reported in the yearly record of the hospital.

The annual report has given the list of the trustees together with their various committees, the consulting physicians, the medical board, the house staff and the names of the physicians connected with the out-patient department. Dr. Hurd then briefly chronicled the important events occurring during the year, referred in detail to the changes in the personnel of the staff and pointed out where certain departments needed to expand or where new departments should be created. It is interesting to watch how a suggestion of his would bring forth fruit. In one report he would advise the innovation, in the next it would be briefly stated that tentative plans were under way. The next report would probably say that the building was under construction, and in the report of the following year would be a detailed description of the building together with splendid illustrations, and in addition there would be a succinct report of the addresses given at the dedication of the building. A more detailed report of the proceedings would usually be contained in the hospital BULLETIN or form the theme for an address.

The report of the Training School for Nurses has always been given a prominent part in the superintendent's report and since 1895 there has been a very full report of the colored orphan asylum. Dr. Hurd has always made it a rule to make acknowledgment of gifts to the hospital no matter how small they have been, and since the beginning he has never failed each year to thank the clergy who have held services in the hospital on the Sabbath. The statistical tables relating to the patients treated in the hospital and in the dispensary have been most exact and very full.

The annual reports of The Johns Hopkins Hospital from 1889 to 1911 breathe the very atmosphere of Henry M. Hurd and in no other way can the reader gain a better insight into his make-up and into the tremendous amount of work this splendid medical statesman has accomplished than by reading these records.

A SYNOPSIS OF THE JOHNS HOPKINS HOSPITAL REPORTS FROM 1889 TO 1911

No description of Dr. Hurd's work would be complete without a reference to that splendid Board of Trustees and that rare medical staff with whom he was associated in the early days of the hospital. I have accordingly had the first and second pages of the first report reproduced. All who were fortunate enough to have been connected with the hospital in the early days will never forget that splendid, candid, whole-souled face of Miss Isabel Hampton. One never thought of Mr. Emory without instantly associating him with Mr. Joseph Hopkins, and everybody in the hospital, both young and old, looked upon Miss Rachel Bonner as an elder sister.

For convenience I have divided the reports into the regular calendar year, although, as a matter of fact, the hospital year began February 1 and ended January 31.

1889

(May, 1889—January 31, 1890)

Dr. Hurd's first report begins as follows:

To the Trustees of The Johns Hopkins Hospital:

GENTLEMEN.—I present herewith a summary of the operations of the hospital during the past seven and one-half months, or since its opening in May last. It has seemed best, all things considered, to make this first report for the fractional year, so that in future the hospital year may correspond with the fiscal year, which runs from February 1 to January 31.

ORGANIZATION

The organization of The Johns Hopkins Hospital differs in some essential features from that of other general hospitals in the United States. The service is divided into three distinct departments—medical, surgical and gynecological each under a responsible chief with continuous service. The heads of these departments are non-resident, but arrangements are made for them to give as much time to the work of the hospital as the necessities of patients demand.

Each department has a responsible resident physician who has had a long and varied experience in a general hospital, and is abundantly able to fill the place of the chief of the department whenever he is absent from the hospital. Each resident physician has a staff of assistants who give aid in case-taking, surgical operations, clinical notes, examinations of urine, sputum, blood, etc.—also in dispensary work generally. The resident and assistant resident physicians, surgeons and gynecologists, are resident in the hospital.

The dispensary has a chief who directs and arranges the work of the different departments, and each department in turn is under the special direction and control of a responsible head, who takes care of the work and has a continuous service. Each head of a dispensary department has as many assistants as the proper work of his department requires, whose medical work he directs and controls.

The nursing work of the hospital is under the charge of the superintendent of nurses, who also acts as the principal of the training school. She has the responsibility of the management of the nurses' home and the instruction of nurses. She selects and accepts probationers, prescribes courses of study and arranges duties. She supervises all nursing-work.

The purchase and delivery of provisions and the cooking, distribution and serving of food, are placed in the hands of a purveyor, who is made responsible for this branch of hospital work.

The care of rooms and buildings and the oversight of the work of the laundry come upon the matron, who is charged with the duty of purchasing bedding, dry goods, clothing, household and laundry supplies. In addition to these offices there is a comptroller of accounts, who supervises the receipt of money and the payment of bills; an apothecary, who purchases medicines and prepares and delivers prescriptions; a supervisor of grounds, who looks after all outside labor; and an engineer, who has the care and oversight of the engines, boilers, filters, pumping apparatus, machinery, warming and ventilating apparatus, water-tanks, sewers, water-closets, lavatories, steam-cooking apparatus, water, gas, electrical and steam distribution.

HISTORICAL

Upon the opening of the hospital in May, 1889, Dr. W. H. Welch had been appointed pathologist, Dr. William Osler, physician-in-chief, and Dr. William S. Halsted, acting surgeon and chief of the dispensary; Dr. Henry A. Lafeur, resident physician, and Dr. F. J. Brockway, resident surgeon; with Dr. H. A. Toulmin, assistant physician, and Dr. George E. Clarke, assistant surgeon.

Subsequently in June Dr. Howard A. Kelly was appointed gynecologist and obstetrician, and Dr. Hunter Robb, resident gynecologist. The value of the services of Dr. Billings in planning and building the hospital cannot be too highly estimated. His foresight as to the future of the hospital, his high ideals of hospital requirements, his familiarity with hospital work and his versatility in adapting means to ends, have done much to bring The Johns Hopkins Hospital to its present state of excellence.

President Gilman's services as an organizer were of great value. By an unusual occurrence of events it was possible for him to bring the university idea into hospital management, and to give to the inauguration of the hospital enterprise a breadth and liberality which it might have lacked had it been exclusively organized by a purely hospital officer.

COURSES OF MEDICAL INSTRUCTION

Beginning with January 6 of the present year [1890] courses of postgraduate instruction in medicine, surgery and gynecology have been inaugurated at the hospital. Daily lectures have been given in the clinical amphitheatre, and clinics in medicine, surgery and gynecology have been given three times a week, at which time the wealth of clinical cases afforded by the hospital and dispensary have been utilized. Rare opportunities to study diseases have been afforded in the dispensary and the hospital wards; and to witness surgical operations in the private operating rooms.

LABORATORIES

The work of the pathological laboratory, formerly carried on by the university, was assumed by the hospital September 1, 1889. No change, however, has been made in any of its arrangements or courses of study, and the work of instruction and original research has gone on as in former years. The pathological material afforded by the hospital has proven unusually rich. It has been most carefully and thoroughly studied by Professor Welch and Drs. Councilman and Abbott.

The clinical laboratory has been in successful operation under the direction of Professor Osler. Analyses of the blood have been made carefully and systematically as a matter of routine, both to determine its constitution and to ascertain the presence of malarial or other organisms and parasites.

The hygienic laboratory has also been equipped and made ready for practical work under the direction of Dr. Billings and Dr. Abbott. Its work thus far has been confined to meteorological observations, the study of ventilation, the analysis of ground-air, and the bacteriological examination of water.

THE TRUSTEES AND MEDICAL STAFF OF THE JOHNS HOPKINS HOSPITAL IN 1889.

These are facsimile pages from the first annual report of the Hospital giving the Trustees, Consulting Physicians, Medical Board and Hospital Staff at that time.

TRUSTEES.

1889-90.

President:

FRANCIS T. KING.

Treasurer:

JOSEPH MERKEFIELD.

Secretary:

LEWIS N. HOPKINS.

Members of the Board:

GEORGE WILLIAM BROWN,	CHARLES J. M. GWINN,
JAMES CAREY,	LEWIS N. HOPKINS,
GEORGE W. CORNER,	FRANCIS T. KING,
WILLIAM T. DIXON,	ALAN P. SMITH, M. D.,
GEORGE W. DOBBIN,	C. MORTON STEWART,
JOSEPH P. ELLIOTT,	FRANCIS WHITE.

COMMITTEES.

Executive Committee.

GEORGE W. CORNER,	FRANCIS T. KING, <i>ex officio</i> ,
GEORGE W. DOBBIN,	ALAN P. SMITH,
	FRANCIS WHITE.

Finance Committee:

GEORGE W. CORNER,	FRANCIS T. KING, <i>ex officio</i> ,
WILLIAM T. DIXON,	FRANCIS WHITE.

Building Committee:

GEORGE W. CORNER,	FRANCIS T. KING, <i>ex officio</i> ,
GEORGE W. DOBBIN,	ALAN P. SMITH,
	FRANCIS WHITE.

CONSULTING PHYSICIANS.

ALAN P. SMITH, M. D.,	representing Hospital Trustees,
JAMES CAREY THOMAS, M. D.,	representing University Trustees,
I. E. ATKINSON, M. D.,	T. S. LATIMER, M. D.,
S. C. CHEW, M. D.,	F. T. MILES, M. D.,
F. DONALDSON, M. D.,	G. W. MILTENBERGER, M. D.,
W. T. HOWARD, M. D.,	L. McLANE TIFFANY, M. D.,
C. JOHNSTON, M. D.,	W. C. VAN BIBBER, M. D.,
	H. P. C. WILSON, M. D.

MEDICAL BOARD.

ALAN P. SMITH, M. D.,	representing Hospital Trustees,
JAMES CAREY THOMAS, M. D.,	representing University Trustees,
W. S. HALSTED, M. D.,	HOWARD A. KELLY, M. D.,
HENRY M. HURD, M. D.,	WILLIAM OSLER, M. D.,
	WILLIAM H. WELCH, M. D.

HOSPITAL STAFF.

Superintendent:

HENRY M. HURD, M. D.

Physician:

WILLIAM OSLER, M. D.

Resident Physician:

HENRY A. LAFLEUR, M. D.

Assistant Resident Physicians:

HARRY TOULMIN, M. D.,

D. MEREDITH REESE, M. D.

Surgeon:

WILLIAM S. HALSTED, M. D.

Resident Surgeon:

F. J. BROCKWAY, M. D.

Assistant Resident Surgeon:

GEORGE E. CLARKE, M. D.

Gynecologist and Obstetrician:

HOWARD A. KELLY, M. D.

Resident Gynecologist:

HUNTER ROBB, M. D.

Assistant Resident Gynecologists:

W. W. FARR, M. D.

A. L. GHRISKEY, M. D.

Pathologist:

WILLIAM H. WELCH, M. D.

Associate in Pathology:

W. T. COUNCILMAN, M. D.

Assistant in Bacteriology and Hygiene:

ALEXANDER C. ABBOTT, M. D.

OUT-PATIENT DEPARTMENT.

Chief of the Dispensary:

WILLIAM S. HALSTED, M. D.

1. *Department of General Medicine:*

WILLIAM OSLER, M. D.

2. *Department of Diseases of Children:*

WILLIAM OSLER, M. D., and W. D. BOOKEE, M. D.

3. *Department of Nervous Diseases:*

WILLIAM OSLER, M. D., and H. M. THOMAS, M. D.

4. *Department of General Surgery:*

W. S. HALSTED, M. D., assisted by J. M. T. FINNEY, M. D.

5. *Department of Genito-Urinary Diseases:*

W. S. HALSTED, M. D., and JAMES BROWN, M. D.

6. *Department of Gynecology:*

H. A. KELLY, M. D., assisted by HUNTER ROBB, M. D.

7. *Department of Ophthalmology and Otology:*

S. THEOBALD, M. D., and R. L. RANDOLPH, M. D.

8. *Department of Laryngology:*

JOHN N. MACKENZIE, M. D.

9. *Department of Dermatology:*

R. B. MORISON, M. D.

MISS ISABEL A. HAMPTON, *Superintendent of Nurses and Principal of the Training School.*

L. WINDER EMORY, *Purveyor.*MISS RACHEL A. BONNER, *Matron.*STANLEY HUTCHINS, *Comptroller of Accounts.*

THE NURSES' TRAINING SCHOOL

The Nurses' Training School was formally opened in October, 1889. A full report of this momentous occasion is given by Dr. Hurd in the first number of THE JOHNS HOPKINS HOSPITAL BULLETIN published on December 1 of that year. After a short address by the president of the Board of Trustees, Mr. Francis T. King, Miss Hampton spoke at length on "The Aims of The Johns Hopkins Hospital Training School for Nurses," and was followed by Dr. Hurd who took as his theme "The Relation of the Training School for Nurses to The Johns Hopkins Hospital." I quote briefly from his address on that occasion:

The beneficent work of The Johns Hopkins Hospital antedates by many years its formal opening in May last. From its inception in the mind of its founder, and the subsequent elaboration of the idea by the trustees so wisely chosen by him—during the preparation of its plans and in the whole course of its erection—from the first foundation stone to the last tile upon the roof, it has constantly been fulfilling its mission. It has all along stimulated hospital construction to an unprecedented degree. From a personal knowledge of hospitals east and west, I do not hesitate to say that there is not a single hospital in this broad land which has not felt the influence of its construction, either directly or indirectly, or has not been energized by its example to make more perfect provision for the care and treatment of sick people. It has taught hospitals the practical application of the laws of hygiene to heating, ventilation, house drainage, sewerage and hospital construction in general. It has commanded attention to the importance of sunlight and air space, and to the absolute necessity of an abundant supply of pure air to each individual—a supply properly tempered to meet the varying conditions of summer heat and winter cold. The cardinal principle of the hospital has been to give the sick the most perfect hygienic surroundings attainable in a city. It has so prepared the way for better provision for the comfort of the sick, whether rich or poor, that the public now demand it. So great, in fact, has been the force of its example for good, I do not hesitate to say that had the hospital never received or treated a single patient, the work it has already accomplished in showing the way to better hospital construction would have fully justified the expenditure of every dollar it cost.

To-day we are assembled to witness the inauguration of one of the departments of this hospital which we hope will influence in a similar manner, even if not in an equal degree, training schools for nurses throughout the country. This school has been established in compliance with the instructions of the founder of the hospital, in the following language: "I desire you to establish in connection with the hospital a training school for female nurses. This provision will secure the services of women competent to care for the sick in the hospital wards, and will enable you to benefit the whole community by supplying it with a class of trained and experienced nurses." The Board of Trustees has carried into effect this injunction in no grudging manner. No school in this country has been more worthily housed or more fully equipped for class-room and practical work and none has ever started out with broader views or more comprehensive plans for the proper training of nurses.

What has the hospital a right to expect from the pupils of this school?

1. They should have an adequate conception of the responsibilities assumed by the nurse when she enters the school. The hands of a nurse are a physician's hands lengthened out to minister to the sick. Her presence at the bedside is a trained vigilance supplementing and perfecting his watchful care; her knowledge of the patient's condition an essential element in the

diagnosis of disease; her management of the patient, the practical side of medical science. If she fails to appreciate her duties the physician fails in the same degree to bring aid to his patient.

2. The nurse should have an enthusiasm in the work of nursing. No one should assume the work without feeling it to be of all occupations the one best suited to the tastes and capacity of the individual. Nursing to be well done should be entered upon with an "enthusiasm of humanity" which will lighten every hardship, and render the nurse happy and contented in her chosen calling.

3. She should consider nursing a profession and view it as a life work. It is not a trade, nor an occupation solely, nor a means of support simply, but a vocation which brings into activity the best sentiments of the human heart and enlists the finer sympathies of our better natures.

4. She should seek to fit herself to be a teacher of others. It should be her ambition to learn the duties of her calling that she may become competent to impart instruction. From this school as from a center of knowledge should go forth graduates to found similar schools throughout the land.

5. For her highest usefulness a nurse should have a capacity for sustained mental effort. Having chosen her life work and proven her fitness for it by a satisfactory period of probation, she should pursue her vocation "without haste, without rest," steadily, persistently and courageously, with a mental equipoise which keeps constantly in view a high ideal of excellence. The sweetest rewards of earth come to earnest effort and faithful accomplishment in lines of philanthropic work. They are not gained by fitful toil or half-hearted endeavor.

Let there may be a misconception I ought to add that enthusiasm in work, devotion to duty, unresting fidelity to high ideals of efficiency, keen humanitarian impulses and love of scientific truth, cannot and must not be considered obligations peculiar to nurses. The trustees and officers of the hospital accept similar obligations for themselves, and expect equal enthusiasm and devotion from all connected with the hospital in any responsible capacity.

What, on the other hand, has the pupil in the training school a right to expect from all who are connected with the hospital?

1. The pupil nurse has reason to expect, and should receive, the respect, confidence and coöperation of every right-minded person.

2. She should enjoy every facility for securing instruction, and an opportunity to obtain a higher training in every branch of knowledge which promises to increase her efficiency and usefulness.

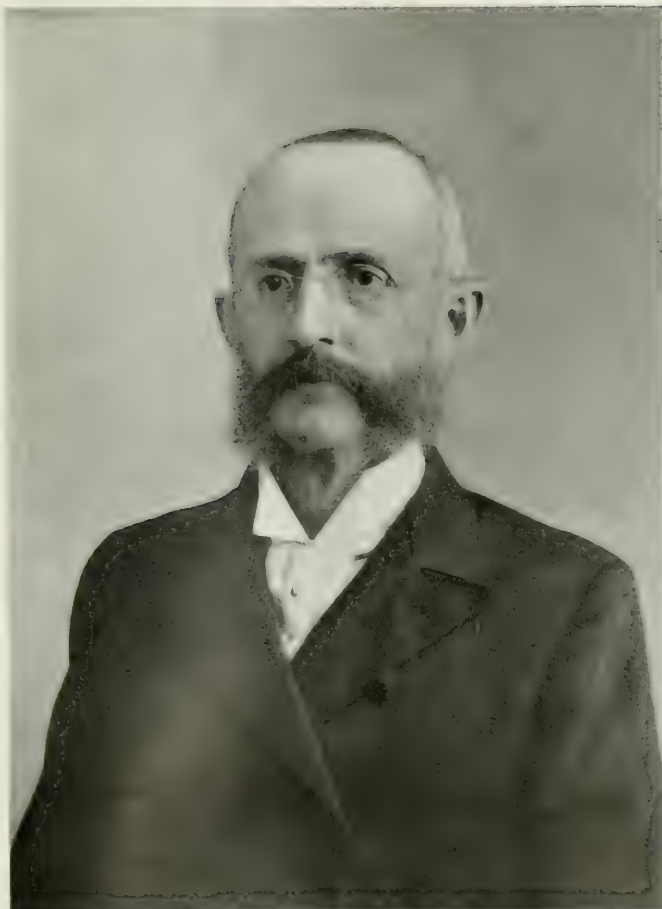
3. She should have proper hours for work, proper hours for study and recreation, pleasant apartments, healthful surroundings, refining associations and every incentive to effort, and every aid to accomplishment of her work.

Many hopes cluster about this training school. The work of many years of patient labor spent in construction is over. The scaffold has been swept away, and the completed edifice stands before us. The work of the hospital cannot be complete until this school is open and in successful operation. The poor of Baltimore in their homes, suffering for lack of proper nursing and adequate attention, look to this school for a solution of the problem of district nursing among the poor. The homes of the wealthy need no less the skilled nursing which this school aims to supply. The trustees and officers of the hospital welcome the school and bid it God-speed.

PUBLICATIONS

In the first annual report Dr. Hurd says:

There has been established, as an organ of the hospital, a monthly publication known as THE JOHNS HOPKINS HOSPITAL BULLETIN, which is to contain announcements, programs, reports



DR. HENRY M. HURD WHEN HE CAME TO THE JOHNS HOPKINS
HOSPITAL IN 1888

of societies and minor medical contributions. The BULLETIN has met with much success and seems to have found a place in medical literature. In addition to the BULLETIN a volume of *Hospital Reports* is published in fasciculi which will constitute a volume of about 500 pages during the year 1890. The first fasciculus contained 64 pages, and had the following list of articles: "On Fever of Hepatic Origin, Particularly the Intermittent Pyrexia Associated with Gall-Stones," by Dr. Osler. . . .

Through the medium of THE JOHNS HOPKINS HOSPITAL BULLETIN the numerous activities of the hospital have been duly chronicled and many important events have been recorded. The numerous discoveries in the various departments have been brought to the notice of the medical world through this journal. It has been a faithful mirror of The Johns Hopkins Hospital and its establishment was one of the most important moves ever made by the hospital. It has enabled the institution to tell the civilized world promptly just what it has accomplished. The *Johns Hopkins Hospital Reports* contain the lengthy articles—those that are too extensive for a monthly journal. They now comprise 18 volumes.

Dr. Hurd started both the BULLETIN and the *Reports* and was editor of both from the initial issue until he relinquished his position in 1911. He was the editor in every sense of the word. Many of the articles which were rather crude in their English construction were entirely recast by him. Any member of the staff who wandered into the superintendent's office late at night when all was quiet or on a Sunday afternoon would find Dr. Hurd busily engaged in correcting galley proofs for the BULLETIN or for the *Reports*.

Both of these publications possess a dignity and style rarely noted in medical periodicals. The printing has been good, the illustrations excellent and the text remarkably free from typographical errors.

The Hopkins BULLETIN and the *Reports* are to be found in medical libraries the world over. Dr. Hurd deserves the lion's share of credit for the marked success of these publications.

SOCIETIES

In the first report Dr. Hurd refers to the medical societies of the hospital.

A flourishing hospital medical society has been established under the direction of Dr. Welch, which meets bi-monthly and is regularly attended by members of the hospital and dispensary staff. At these meetings papers are read, patients are exhibited, morbid pathological specimens are presented and the results of original investigations in the clinical, pathological and hygienic laboratories are reported. These meetings have been of great value, and the amount of work which has been done compares most favorably with that accomplished by any other similar society.

A Journal Club, composed of members of the hospital and dispensary staff, also meets bi-monthly. At these meetings the current literature in the various departments of medicine, surgery and gynecology is presented in abstract by persons previously appointed to report from these departments. This enables all members of the staff to keep fully informed as to what is being accomplished by workers in every branch of medical science with the least expenditure of time.

In November, 1890, a Historical Club was organized to hold monthly meetings for the study of medicine in its historical

aspects. These meetings have been well attended and have proven interesting and profitable.

The Historical Club still continues. Scattered throughout the various volumes of THE JOHNS HOPKINS HOSPITAL BULLETIN are many articles which were read at the Historical Society. They are of much interest and value.

1890

(February 1, 1890—January 31, 1891)

In the report for the year ending January 31, 1891, Dr. Hurd refers to the work of the hospital among the poor of Baltimore and emphasizes the fact that care must be taken to see that people who are financially able should not be given free treatment:

The added experience of a year has demonstrated the necessity of the medical, surgical and gynecological work which this hospital is doing among the poor of Baltimore. The free work has constantly grown in importance and usefulness since the opening of the hospital and hundreds of poor people have received relief who could not have obtained it otherwise. This work has been done cheerfully and ungrudgingly both among hospital and dispensary patients. It is evident, however, that some persons who apply for gratuitous advice and prescriptions in the dispensary, and free beds in the hospital are not objects of charity, and should not receive the benefits of the institution.

In some of the New York hospitals the names of all persons applying for relief, when any doubt exists as to the propriety of granting it, are reported to the Charity Organization Society, and a systematic investigation is made by an agent of this society. After a careful review of the whole subject I am strongly of the opinion that the time has come when an arrangement should be made with the Charity Organization Society of Baltimore, whereby all suspected cases may receive a prompt investigation. It demoralizes any man to receive as a gift what he is able to pay for wholly or in part. Indiscriminate and haphazard charity begets habits of improvidence and of wastefulness, if not of actual vice among its recipients.

In addition to the evil effect upon the community of indiscriminate charity there is also danger of doing injustice to the profession of medicine, which numbers among its members so many persons actively engaged in charitable work. Neither the hospital nor dispensary should interfere with the sources of support of these men by affording free medical or surgical treatment to those who are able to pay for it.

In this connection mention may be made of the excellent provision which exists at this hospital for the accommodation of private or pay patients—a provision which is not excelled in any general hospital in this country.

Dr. Hurd in the report also refers to the Training School for Nurses:

Each month demonstrates the value and necessity of the work of the Training School for Nurses. The school is developing a new field of usefulness for the young women of Baltimore and Maryland and is growing in popular favor. The dignity and importance of the profession of nursing were never so well appreciated in this community as now.

From the early days of the hospital to the present it has been a matter of frequent comment that for intellectual refinement and for mental capacity few if any hospitals in America have been as fortunate as The Johns Hopkins Hospital in the personnel of its Training School for Nurses.

1891

(February 1, 1891—January 31, 1892)

The report for the year ending January 31, 1892, contains the names of the first class of nurses who graduated from the training school. Among them are Mary E. Gross (Mrs. John M. T. Finney), Georgie M. Nevins the superintendent of Garfield Hospital, Washington, D. C., M. Adelaide Nutting who later became superintendent of nurses in The Johns Hopkins Hospital Training School and who is doing such excellent work as professor in the Teachers' Training School at Columbia University, New York. This list also contains the name of Susan C. Read (the late Mrs. William Sydney Thayer).

1892

(February 1, 1892—January 31, 1893)

MEDICAL INSTRUCTION

In the report for the year ending January 31, 1893, Dr. Hurd makes a most important announcement relative to the opening of The Johns Hopkins Medical School.

By the endowment of the medical school through the generosity of Miss Garrett and others, the university is now in a condition to assume the responsibility of medical instruction, and commencing with October 1, 1893, both graduate and other work will cease on the part of the hospital. It is gratifying, in the review of the past three years, to notice that women have not in any respect proven a disturbing element. They have pursued their work under the same conditions as men, and have done faithful, honest and successful work. Although the hospital ceases to do any more medical teaching, the fact that the governing idea in its erection was the promotion of medical teaching cannot be lost sight of. The construction of the wards, the location of the laboratories, the arrangement of the dispensary and amphitheater, the divers systems of heating and ventilating, and the facilities for their demonstration, all point to a preconceived plan that the hospital should do its share in the work of practical instruction. It is confidently believed that no other hospital in the United States is better equipped to do medical teaching, or in its brief career has done more thorough and suggestive work. The same faithful work will be continued by the same men, under the direction of the university in future, as a part of the curriculum of the medical school.

LYING-IN AND CHILDREN'S WARDS

The approaching opening of the medical school renders it important that no time be lost in arranging for the erection of a lying-in ward, to provide for the proper instruction of medical students and nurses. In many respects it seems most desirable that this ward be situated adjacent to the hospital, so that nurses may be readily provided, and yet far enough removed to render it free from the stir and publicity of a large general hospital, and a numerously attended out-patient department. This building ought eventually to be built upon a well-approved plan, and should furnish ample accommodations for women who are awaiting confinement, for parturient women, and for those who suffer from any form of puerperal infection.

A children's ward, separate and distinct from other wards, must be erected. Such a ward alone will give children the proper opportunity for comfort and recovery.

The children are now well provided for in the Harriet Lane Home. After long years of waiting it is a pleasure to know

that in the near future the obstetrical department is to have adequate and most satisfactory accommodations.

1893

(February 1, 1893—January 31, 1894)

In the report for the year ending January 31, 1894, Dr. Hurd describes the colored ward:

The colored ward, of which mention was made in the last report, has also been erected during the year and is now ready for the reception of patients. It consists of two stories surmounted by a half story.

This addition to the hospital has been of great value as it brings all the colored patients under one roof instead of having them scattered in various portions of the institution.

Dr. Hurd then refers to important changes in the library.

The opening of the medical school, and the increased demand for medical books on the part of medical students, have rendered it desirable to pay special attention to the library of the hospital. Miss Thies, who has received a careful training in the Enoch Pratt Free Library, has accordingly been employed at the joint expense of the university and hospital to catalogue and arrange the collections which have grown rapidly during the year. It is evident that by the close of another year the shelving will be filled, and no more room will be available for future additions. It consequently becomes important to know how increased accommodations can be secured.

In this connection it seems eminently proper to refer to the great advantages which the medical officers of the hospital and the students in our medical courses have derived from the proximity of the library of the Surgeon General's Office. The enlightened policy of this library, whereby valuable books of reference otherwise unattainable are loaned to the hospital under satisfactory guarantees against loss, cannot be too highly praised. The medical officers of the hospital, and the instructors and students of the medical school, are under many obligations for the uniform promptness and courtesy of those who have charge of this unrivaled collection of books in meeting the frequent demands made upon them.

THE WHITE ROSE FUND

By the generous act of Mrs. W. E. Woodyear, of Baltimore, the "White Rose Fund" has been established and the sum of \$5000 has been placed at the disposal of the trustees, the interest of which is to be used for the comfort and happiness of sick children. It was not proposed to endow a bed or to establish a charity, but to use the income of the fund in such a way as to promote the comfort and happiness of poor, sick children who occupy beds in the public wards of the hospital.

It was the intention of the liberal donor to provide means by which flowers, books, pictures, excursions, music and other means of amusement could be afforded for the children in a more liberal manner than would be practicable if these extra expenses were paid out of the income of the hospital.

It is doubtful if any gift to the hospital, no matter how large, has yielded more downright satisfaction to the donor than this gift has. Year after year Dr. Hurd has referred to how much it has meant to the children and what added pleasures this fund has made possible. He has always been most enthusiastic when speaking of it in report after report. It reminds one of a thread of gold carried through from year to year. Mrs. Woodyear gave this money in memory of her little daughter, Rose Blanche Woodyear.

1894

(February 1, 1894—January 31, 1895)

In the year 1894 several important advances were made.

Experience having shown that the work of the pathological department was of great value and importance to every other department, it was decided by the trustees, after a thorough consideration of the subject by the medical board, to organize this department, and to give it an equal standing in the medical staff by appointing a resident pathologist and an assistant resident pathologist. In consequence of this action, Dr. Simon Flexner, associate in pathology in the medical school, was appointed resident pathologist, and Dr. L. F. Barker, the associate in anatomy, was appointed assistant resident pathologist.

As far as is known at present, this is the first instance where similar officers have been appointed with staff standing in connection with any hospital in the United States.

OUT-PATIENT OBSTETRICAL SERVICE

This service has been placed under the immediate charge of Dr. J. Whitridge Williams, the associate in obstetrics in The Johns Hopkins Medical School, who has received the appointment of assistant obstetrician to The Johns Hopkins Hospital. Dr. G. W. Dobbin has been appointed an additional assistant in the gynecological department to look after this work in a special manner, both in the dispensary and in attending patients in their homes. It is contemplated that poor patients expecting to be confined, and unable to pay the expenses of a physician, shall visit the dispensary to arrange for the services of the resident obstetrician. In arranging for this service it is hoped to be able to bring relief to patients who require the services of a physician, and to furnish the attention of a skilled nurse during the first 24 hours following confinement. It is expected that this service will eventually grow into a branch of district nursing.

In this report Dr. Hurd refers to the resignation of Miss Hampton.

Shortly after commencement exercises in June last, 1894, Miss Hampton, who had been the superintendent of the training school ever since its opening, tendered her resignation. Her services to the school had been of great value, and her resignation and relinquishment of all training school work must be regarded a serious loss to trained nursing throughout the country.

Upon her resignation, Miss M. A. Nutting, who had been her assistant for the previous two years, received the appointment of acting superintendent. Subsequently, in December last, she was appointed superintendent, and given leave of absence for eight months from February first to visit other hospitals and training schools in this country and Europe, to see their methods and to perfect herself in nursing work.

THE COLORED ORPHAN ASYLUM

In Dr. Hurd's report for the year ending January 31, 1895, we find the first report of the colored orphan asylum.

By the will of the founder of the hospital, the erection and maintenance of a colored orphan asylum was enjoined, and provision was made for its support out of the income of the hospital fund.

A tract of land on Remington Avenue and King Street has been purchased as a permanent site for The Johns Hopkins Colored Orphan Asylum, and the children have been removed to their new home.

A detailed report of the committee on the colored orphan asylum follows that of Dr. Hurd.

1895

(February 1, 1895—January 31, 1896)

In Dr. Hurd's report for the year ending January 31, 1896, we find an account of an addition to the dispensary:

In accordance with the recommendation of the medical board, the trustees erected, during the summer of 1895, in connection with the dispensary four class-rooms for the accommodation of classes from the medical school.

Dr. Hurd in this report also records the death of one of the most picturesque members of the hospital family:

Upon the 16th day of October, 1895, Mr. L. Winder Emory, who had discharged the duties of purveyor with conspicuous ability and fidelity, died suddenly of angina pectoris. The vacancy thus created was filled January 1, 1896, by the appointment of E. H. Read, of Baltimore, who immediately entered upon the discharge of his duties.

1896

(February 1, 1896—January 31, 1897)

THE CLINICAL LABORATORY

In the report for the year ending January 31, 1897, Dr. Hurd refers to the new clinical laboratory:

By an unexpected gift of \$10,000 from a generous donor, whose name we are prohibited to mention, it has been practicable to erect a large and convenient clinical laboratory for the use of the hospital and medical school between the amphitheatre and dispensary. This portion of the building, which was formerly one story in height, has now been raised to three stories, and the additional room furnishes ample accommodation for medical classes.

Miss Nutting's report to the superintendent for the year 1896 announces the inauguration of the three-year course in the Training School for Nurses.

The demand for information concerning the school remains about as usual:

The number of written applications for	
circulars	1143
Applicants formally considered	160
Accepted applicants	61

Among the acknowledgments for the year ending January 31, 1897, Dr. Hurd mentions Mr. Spence's gift of a reproduction of Thorwaldsen's statue of Christ:

One of the most noteworthy and appropriate gifts which the hospital has ever received is a reproduction of Thorwaldsen's celebrated statue of Christ, by Stein of Copenhagen, which has been placed in the rotunda through the liberality of William Wallace Spence of Baltimore. A full account of the interesting exercises at the unveiling of this statue, together with the addresses delivered on that occasion, was published in the BULLETIN for January, 1897.

The superintendent's report for the year ending January 31, 1897, gives for the first time the "By-Laws, Rules and Regulations of The Johns Hopkins Hospital." A perusal of this 18-page article gives a most illuminating idea of the inner working of this hospital.

*The reader will be interested to know that Mr. Spence rounded out his century—he died a short time after his 100th birthday.

1897

(February 1, 1897—January 31, 1898)

In 1897 the first class of The Johns Hopkins Medical School received their degrees from The Johns Hopkins University, and the 12 students who stood highest in their class were eligible for positions in the hospital. Dr. Hurd in his report for the year ending January 31, 1898, says:

Beginning with the first of September, 1897, 12 members of the graduating class of The Johns Hopkins Medical School are in future to be appointed resident medical officers. These physicians are divided into three groups, and serve four months in each department of hospital service, the service being determined by lot. In this manner each resident medical officer secures four months service in medicine, surgery and gynecology.

In addition to these resident medical officers, the resident physician, surgeon and gynecologist each is supplied with a first and second assistant, who are appointed from those who have had previous hospital experience. The working of this plan has thus far been satisfactory.

In accordance with this arrangement the following-named persons were appointed resident medical officers*: Drs. G. L. Hunner, J. F. Mitchell, O. B. Pancoast, L. P. Hamburger, Thomas R. Brown, E. L. Opie, R. P. Strong, W. G. MacCallum, W. S. Davis, I. P. Lyon, C. A. Penrose and Mary S. Packard.

The rotation system was abandoned after a few years.

* Taken as a whole this was the most remarkable group that has ever graduated from The Johns Hopkins Medical School. Several of them have international reputations.

Dr. Walter S. Davis died in September, 1898, and in the Annual Report of the Hospital for that year Dr. Hurd paid a fitting tribute to his worth.

Recently Dr. Clement Andariese Penrose, another member of this group, died. He received his A. B. degree from The Johns Hopkins University in 1893 and immediately entered the Medical School. After his year as intern he located in Baltimore and in a few years was recognized as one of the most promising of the younger physicians.

In 1903 he served as Vice-Director and Surgeon of the Bahama Expedition. His report of the medical conditions noted on the trip is very interesting. The most valuable paper was that on Leprosy. This paper graphically depicted the deplorable condition existing in the Bahamas due to leprosy and to degeneracy resulting from close intermarriage.

In the spring of 1917 he was appointed Chairman of the Baltimore Food Economy Commission and did much to further food conservation.

In August 1917 he was commissioned major in the United States Army and was sent by the surgeon general to make an exhaustive study on army sanitation in the English and French armies. General Gorgas in speaking of Dr. Penrose's report said: "This report has been of great value to the Medical Department of the United States Army."

After completing his work on sanitation he took charge of a three-hundred bed hospital at Gondricourt, France. Here he contracted a septic bronchitis which nearly caused his death at the time. He partially recovered but was left with an impaired heart.

He returned to America late in December and for a time was able to resume his practice. In March 1919 the infection again became pronounced. He gradually lost ground and died early on the morning of July 4, 1919.

Penrose was an excellent medical consultant, a man of rare judgment, beloved by his patients and a loyal friend. His death was a great loss to the citizens of Baltimore.

Dr. Hurd's report for this year also contains an account of the addition to the gynecological operating room rendered possible by the generosity of Dr. Howard A. Kelly, who gave \$5000 to assist in defraying the expenses.

In Dr. Hurd's report for this year scholarships and honorable mention in the Training School for Nurses are recorded for the first time.

Dr. Hurd says:

The experience of another year has demonstrated the feasibility and desirability of extending the course of training of nurses from two to three years. The changes in the course of study have enabled nurses to spend more time in learning the fundamental branches of their work, and the shortening of hours of duty has enabled them to bring greater freshness and vigor of mind to their studies and regular duties. The result has been to improve the standard of nursing, and to give a greater state of efficiency to the school than it has ever previously had.

1898

(February 1, 1898—January 31, 1899)

In his report for the year ending January 31, 1899, reference is made to an incident that cast a pall over the hospital family. It is vividly remembered to this day:

It is my sad duty to report the death of Dr. L. E. Livingood who had filled the position of assistant resident pathologist for two years, and who had secured a leave of absence to go to Europe for further study. He left his duties July 1 and was drowned a few days after in the destruction of the ill-fated steamer *La Bourgoyne*. He possessed unusual ability, great industry and a finely trained mind, a combination of qualities which gave every promise of success as a teacher and research worker. In his death the hospital and the medical school have experienced a severe loss.

The hospital lost another of its young medical men during this year, Dr. Walter S. Davis died of Addison's disease on September 27, 1898. In referring to him Dr. Hurd says:

Dr. Davis was full of energy and enthusiasm, and during his medical course and his year of hospital residence showed himself thorough in his work, conscientious in the discharge of duties and efficient and faithful in all he attempted to do. His teachers and associates anticipated high success for him in his chosen profession, and all lament his untimely death.

A glance through the list for this year of those who secured scholarships in nursing is particularly interesting. Among the names in the senior class is Elsie Lawler, our present superintendent of nurses. In the junior class the name of Agnes Hartridge, one of the present assistant superintendents of the hospital. The steady advancement of these two members of the training school for nurses is ample proof that Miss Nutting made no mistake in her selection of her pupils meriting scholarships.

1899

(February 1, 1899—January 31, 1900)

GRADUATES FILLING POSITIONS AS SUPERINTENDENTS OF TRAINING SCHOOLS FOR NURSES

One of the most interesting items in the report for the year ending January 31, 1900, is a list of the graduates of the

training school who are filling positions as superintendents of training schools for nurses. This list contains the names of 24 graduates of The Johns Hopkins Training School who are now themselves the heads of training schools. Nothing could show more graphically how much the graduates of this school are appreciated throughout the United States and Canada.

1900

(February 1, 1900—January 31, 1901)

In the report for the year ending January 31, 1901, Dr. Hurd refers especially to Volumes VIII and IX of *The Johns Hopkins Hospital Reports*:

The past year has been one of considerable activity in the publications of the hospital. Volume VIII of the *Reports*, containing exhaustive studies by Dr. Osler and his staff in typhoid fever, has recently been published, and Volume IX, which contains 38 elaborate articles prepared originally by his students to celebrate the 25th anniversary of the doctorate of Professor W. H. Welch, the pathologist of the hospital, was published in April last and constitutes a volume of nearly 1100 pages. In point of excellence of matter and thorough presentation of scientific work the volume is fully equal, if not superior, to any of similar character ever published in this country.

In addition, the BULLETIN has been regularly published with increasingly valuable contributions each month. Volume XI which was completed with the December issue, contains 340 pages and numerous illustrations.

1901

(February 1, 1901—January 31, 1902)

In the report for the year ending January 31, 1902, Dr. Hurd again refers to the great value of THE JOHNS HOPKINS HOSPITAL BULLETIN and of the *Reports*. He says:

Volume X of *The Johns Hopkins Hospital Reports* is in progress and will be completed during the present summer. The BULLETIN of the hospital has been issued monthly during the year and has now reached an annual volume of nearly 400 pages. It is gratifying to observe how extensively it is circulated and quoted both in this country and in Europe. It is evident that this publication has made a permanent place for itself in medical literature and our publishers inform me that the series of volumes is already in active demand to supply libraries. The papers presented in it during the past 12 years form, in fact, a good commentary upon the advance of scientific medicine in America.

During the past year, it may be added, the volume of the BULLETIN has furnished upward of 900 octavo pages of reading matter.

Dr. Hurd also mentions the substantial addition to the public gynecological ward:

During the year, in order to furnish additional accommodations for patients recovering from gynecological operations, and to secure facilities for an examining room and laboratory in connection with this ward, Dr. Kelly, with great liberality, gave to the hospital the sum of \$10,000. This sum has been expended in building upon the north side of the public gynecological ward, a large two-story annex which affords accommodations for 12 patients.

The superintendent also gave a complete list of the larger donations made to the hospital from the time of its completion up to the end of 1901.

1902

(February 1, 1902—January 31, 1903)

From Miss Nutting's report to Dr. Hurd for the year ending January 31, 1903, we learn of the esteem in which graduates of the training school are held. This is shown by the large number of requests for nurses to fill important positions in other schools:

Letters requesting us to send our graduates to fill positions as follows:

Superintendents	26
Assistants	6
Head nurses	15

1903

(February 1, 1903—January 31, 1904)

Nearly every hospital board of trustees has its period of anxiety and perplexity wondering just how it will meet its financial obligations. The trustees of The Johns Hopkins Hospital have been men of affairs—men possessing a broad vision—and they have in every instance found their way out of the dilemma. Early in 1904,* however, without a day's warning, their annual income was for the time being markedly impaired. Dr. Hurd in his annual report published early in 1904 refers to this critical period in the hospital's career in detail:

To the Board of Trustees of The Johns Hopkins Hospital:

GENTLEMEN.—The close of the past year of the hospital has been marked by the most serious calamity which has befallen the hospital during its existence. On the morning of February 7, almost before it had been possible to sum up the results of the operations of the previous fiscal year, which closed February 1, a general conflagration swept over the city of Baltimore and proved most disastrous to the real and lease-hold property of the hospital. During the fire 64 stores, warehouses and office buildings, widely scattered in the business portion of the city, representing an assessed valuation of more than a million and a quarter dollars, were destroyed, entailing a loss of income for at least two years of about \$120,000. A portion of this loss was made up by insurance. In accordance, however, with the policy of the hospital, an insurance had not been secured against a total loss, but merely for a sum which had been deemed sufficient to provide for rebuilding in case of partial destruction by fire. The results, however, proved that such insurance was wholly inadequate to repair the effects of a wide-spread calamity, and a loss of capital funds of between \$300,000 and \$400,000 resulted.

For several weeks thereafter great anxiety was felt lest it should become necessary to curtail seriously the work of the hospital by closing wards and cutting down the staff of nurses and employes. Through the liberality, however, of Mr. John D. Rockefeller, of New York, who had familiarized himself thoroughly with the work of the hospital, its financial standing, and its loss of income and capital, a half million dollars have been placed at the disposal of the trustees to repair these losses and to enable the work to go on without diminution. Never was assistance more timely to the institution. The magnitude of the work of

* As it often requires six months to assemble the data of the preceding year the annual report appears about the middle of the following year; hence the Baltimore fire of February, 1904, was mentioned in the report for 1903.

the hospital and the need of increasing clinical facilities to meet the growing demands of the medical school had hitherto consumed all its income and had left no available fund to meet the unforeseen emergency of rebuilding its warehouses. Hence the peculiarly timely character of the aid afforded by Mr. Rockefeller, and the critical condition of the institution without such assistance. The thanks of the medical staff of the hospital and of the officers of the medical school are due to him for his prompt and generous recognition of the educational work of the hospital.

At a special meeting of the Board of Trustees of The Johns Hopkins Hospital on Thursday, April 7, 1904, the following action was unanimously taken in reference to the gift of Mr. Rockefeller:

"In view of the donation of \$500,000 made to The Johns Hopkins Hospital by John D. Rockefeller:

"Resolved, That the Trustees of The Johns Hopkins Hospital desire to express their grateful appreciation of the gift of Mr. John D. Rockefeller to The Johns Hopkins Hospital, announced to the trustees by his son, Mr. John D. Rockefeller, Jr., in a letter to Dr. William Osler. This munificent donation will enable the hospital to continue its works of charity, medical education, medical research and the training of nurses; and the trustees hope and believe that by a wise use of this donation they will be able to expand and improve the great institution committed to their custody."

The report for the year ending January 31, 1904, contains the following sentence: "In the out-patient obstetrical department there were 285 cases treated, with no deaths." This speaks volumes for the splendid work being done by the obstetrical department.

This year brought another liberal donation to the hospital.

Through the liberality of Mr. Henry Phipps, of Pittsburgh, the sum of \$20,000 has been given to the trustees of the hospital to increase the facilities of the out-patient department for the study and treatment of tubercular patients. It was the wish of the donor that one-half of this sum should be used to construct a separate dispensary for tubercular patients so as to render it possible to segregate these from other patients. It was his further wish that the remaining \$10,000 should be so invested that the income may serve to promote special work and investigation.

In this report Dr. Hurd quotes extensively from a splendid paper by a member of the hospital staff. This article is entitled "The Relation of The Johns Hopkins Hospital to Medical Education and the Promotion of Medical Knowledge." It gives a clear and concise view of the close connection between the work of the hospital and the medical school. It takes up in succession:

1. Construction of the hospital.
2. Medical organization of the hospital.
3. Relation of the hospital to medical education.
4. Relation of the hospital to the advancement of medical knowledge.
5. The treatment of patients.
6. The Training School for Nurses.
7. Relation of the medical school to the university and to the hospital.

This paper should be read by all interested in medical teaching and in hospital management.

In the report for the year ending January 31, 1904, we find the first annual report of the x-ray department. Dr. F. H. Baetjer has been in charge of this department from its incep-

tion up to the present time. He has made an unusual success of this important branch of the work.

In the annual report for 1903 Dr. Hurd has made a splendid innovation. He gives a complete list of the trustees of the hospital from 1867 to the present. There is also a complete list of the officers of The Johns Hopkins Hospital from 1889 to 1903. This list includes not only all the senior members of the staff, but also every resident physician, resident surgeon, resident gynecologist, resident obstetrician, resident pathologist, assistant resident physician, assistant resident surgeon, assistant resident gynecologist, assistant resident obstetrician, assistant resident pathologist, and every house medical officer. It is in reality an up-to-date directory of every medical man who is or has been connected with the hospital since its opening. It will be of the greatest value in succeeding years.

1904

(February 1, 1904—January 31, 1905)

Dr. Hurd in his report for this year refers to the new clinical building.

The amphitheatre and surgical building, to which reference was made in the last report, were completed and made ready for occupancy in October, 1904. A full description was given in the last report, and need not be repeated here.

The building has proven extremely useful, and has added very much to the convenience of the surgeons in their operative work, and has afforded needed facilities for those who are engaged in teaching.

The basement of the building has been fitted up for a genito-urinary clinic, under the charge of Dr. H. H. Young.

The new surgical building and clinical amphitheatre were formally opened on October 5, 1904. Appropriate addresses were made by Henry D. Harlan, president of the Board of Trustees; Dr. Lewis A. Stimson, of New York; Dr. T. Clifford Allbutt, of Cambridge, England; Dr. A. Jacobi, of New York; and Dr. D. C. Gilman, ex-president of The Johns Hopkins University. At the unveiling of the tablet in memory of Dr. Jesse W. Lazear, addresses were made by Dr. James Carroll, of the United States Army, and by Dr. William S. Thayer.

Dr. Hurd in this report also refers to the opening of the Phipps Tuberculosis Dispensary.

The Phipps dispensary was opened with appropriate ceremonies on the 21st of February of the present year. Short addresses were made by Mr. Henry Phipps; Dr. William Osler; Dr. H. M. Biggs, of New York City; and Dr. Henry Barton Jacobs, president of the Laennec Society, a society for the study of tuberculosis.

Mr. Phipps subsequently gave \$5000 to be used for the purchase of books and apparatus and for the endowment of the dispensary. Under the arrangements which were made, the sum of \$10,000 from Mr. Phipps's former donation was used in the construction of the Phipps dispensary, and the remaining \$10,000 was set aside as a permanent endowment.

1905

(February 1, 1905—January 31, 1906)

The effects of the fire were felt for a long period of time, and in Dr. Hurd's report to the trustees for the year ending

January 31, 1906, we find the following reference to the financial stress that was still felt by the hospital:

The work of the hospital during the past year has been attended with unusual cares and anxieties, due largely to the disturbed finances of the institution, consequent upon a diminution of income. When the last report was presented, it was hoped that, by speedy rebuilding, increased rentals from the buildings which were erected might become available at an early day so that the necessity of pinching economy might be removed. Unfortunately, however, the expense and delays of rebuilding, due to the rush to erect a large number of buildings at the same time in the burnt area, rendered it impossible to regain the full income of the hospital during any portion of the year, and we are forced to conclude it with a large deficit. It is hoped that the coming year will be more prosperous.

RESIGNATION OF DR. OSLER

The departure of Professor Osler wrenched the heart-strings of each and all of the Hopkins family. Dr. Hurd in his report said:

In May last Dr. William Osler, who had filled the position of physician-in-chief to the hospital since its opening in 1889, resigned to accept the position of professor of medicine at the University of Oxford. This closed a most faithful, efficient and active service on the part of Professor Osler, covering a period of 16 years. During this time he had given himself untiringly to the work of the hospital and had won reputation as one of the most accomplished clinical teachers in America. Through his energy and foresight the organization of the medical service of the hospital was early perfected, and his long period of service enabled him to fully develop the plans formed upon his coming to the hospital. He was much beloved by his patients and by the members of the medical staff. The trustees in his departure have lost an inspiring and a stimulating personality. It is gratifying to know that he is to return at stated intervals to Baltimore, in order to keep himself in touch with the work of the hospital and of the medical school.

APPOINTMENTS OF DR. BARKER AND DR. THAYER

To fill the vacancy occasioned by the resignation of Dr. Osler, Dr. Lewellys F. Barker, of the University of Chicago, once an intern and later a resident pathologist in the hospital, and for several years a teacher in the medical school, was appointed physician-in-chief, and Dr. William S. Thayer, for many years resident physician at the hospital, and former associate in medicine, was appointed associate physician. Under the experienced guidance of these able men, it is confidently felt that the medical work of the hospital will continue with undiminished efficiency.

The accommodation for children in the past had been totally inadequate and through the cooperation of the trustees of the Harriet Lane Home and those of the hospital it looked as if ample facilities would be afforded.

Miss Helen Skipworth Wilmer, a graduate of The Johns Hopkins Training School for Nurses, gave \$30,000 in memory of her father, and the trustees contemplated using this money in erecting an additional building for the accommodation of the ever-increasing number of pupil nurses.

Dr. Hurd in his report on these projects said:

By the will of the late Mrs. Harriet Lane Johnston, of Washington, a home for invalid children from the state of Maryland has recently been established with an ample endowment, to be known

as the Harriet Lane Home for Invalid Children of Baltimore City. After considerable thought upon the matter, the trustees of the home deemed it wise to establish a working relation between the proposed institution and some well-organized hospital. Accordingly, upon mature consideration on the part of the trustees of The Johns Hopkins Hospital and of the Home for Invalid children an arrangement has been made whereby the home will be placed as a children's hospital for medical and surgical cases upon the grounds of The Johns Hopkins Hospital. The hospital will provide a site for the building free of charge, furnish heat and light, and assume the maintenance and nursing of the children at a specified price. The home will remain under the charge of the Board of Trustees as established by its founder, and an agreement has been made which will insure a wholly harmonious relation between the two institutions.

In December last Miss Helen Skipworth Wilmer of Baltimore, offered to the hospital the sum of \$30,000 to be used to erect a memorial to her father, the late Skipworth Wilmer, Esquire, a prominent citizen of Baltimore, and for a number of years a member of the Board of Trustees of The Johns Hopkins Hospital. Mr. Wilmer, during his entire connection with the hospital, felt a special interest in the education of nurses, and it seems peculiarly fitting that his daughter should thus desire to perpetuate his memory. The trustees have accepted the gift, and propose to erect in connection with the nurses' home an additional building to be used as dormitories for the nurses.

Strangers going to and from the hospital often linger to examine the sun dial and in sunny weather to see how closely their watches tally with the dial.

Mr. George K. McGaw, one of the trustees of the hospital, has placed in the circle upon the terrace immediately in front of the hospital entrance an ornamental bronze sun dial upon a pedestal, after a novel design by Albert C. Crehore, of Yonkers, N. Y., and so arranged as to tell the time during the entire day as well as the time of sun-rise and sun-set throughout the year. This dial from its original design and beautiful workmanship is highly ornamental to the grounds of the hospital.

AWARD AT THE LOUISIANA PURCHASE EXPOSITION

In 1904 the Maryland Commission of the Louisiana Purchase Exposition made an appropriation of \$700 to defray the expenses of transporting and setting up an exhibit of The Johns Hopkins Training School for Nurses at St. Louis.

The exhibit was duly installed under the direction of Miss Ross, and excited much interest among those who visited the exposition. The grand prize, consisting of a diploma and a bronze medal, was awarded by the Board of Awards. Unfortunately, owing to the high price of labor and the difficulties incident to the transportation of the exhibit and fitting it up in St. Louis, an indebtedness of about \$350 was incurred, which was assumed personally by Mr. William A. Marburg, one of the members of the Maryland commission and a trustee also of the hospital.

1906

(February 1, 1906—January 31, 1907)

The report for 1906 was made by Dr. Rupert Norton, who had been appointed acting superintendent during the superintendent's absence. In his report to the trustees Dr. Norton says:

In the absence of Dr. Henry M. Hurd, superintendent, to whom you have granted a year's leave of absence to date from November 1, 1906, I have the honor to submit the following report on the work of the hospital during the year ending January 31, 1907.

Since the last report was presented the hospital has had a most successful financial year, and it looks as though the coming years would be free of many of those cares and anxieties which have troubled the hospital in the past; the present year ends with a small surplus to its credit.

Dr. Norton's report also chronicles the splendid Marburg bequest.

Mr. William A. Marburg, Mr. Albert Marburg, Mr. Theodore Marburg and the Misses Marburg gave to the hospital the sum of \$100,000 in memory of their brother the late Charles Marburg. The money was expended in the erection of a four story private ward called "The Marburg." This building has enabled the hospital to handle many more private patients than was heretofore possible.

DR. HURD'S VACATION

Early in November, 1906 Dr. Hurd commenced his well-merited year's leave of absence. He left for New York and there boarded a steamer for Havana. After a short stay in Cuba he journeyed to Mexico and remained there, visiting various points of interest, until January.

In January he returned to Baltimore, and in a short time left Boston for Europe accompanied by Mrs. Hurd, Miss Hurd and Miss Anna Hurd. Their first stop was at the Azores. They thoroughly enjoyed a visit to Gibraltar and to Algiers. They visited in succession the chief cities of Italy and also went to Sicily. After a stay at Lake Como they went to Switzerland. Here Dr. Hurd left his family and journeyed to England where he renewed many old acquaintanceships and visited the asylums and hospitals. He greatly enjoyed an extended tour through Scotland. Here also he was royally treated.

Leaving Scotland Dr. Hurd rejoined his family in Holland and attended the International Congress of Alienists in Amsterdam.

He returned to America thoroughly rested and greatly pleased with what he had seen during his happy year of leisure. He resumed his hospital duties on November 1, 1907.

1907

(February 1, 1907—January 31, 1908)

In the report for the year ending January 31, 1908, Dr. Hurd refers at length to the Training School for Nurses and dwells especially on the loss the hospital had sustained through the resignation of Miss Nutting.

The training School for Nurses during the past year has been called upon to part with its superintendent and principal, Miss M. Adelaide Nutting, who had ably supervised its work since 1894, when she succeeded Miss Hampton, now Mrs. Robb, upon the resignation of the latter. . . .

Miss Nutting, her immediate successor, graduated from the first class of nurses trained by Mrs. Robb, and subsequently held important teaching positions in the school. Her connection with the school in fact as pupil and teacher covered a period of about 18 years, and during this period she inaugurated many improvements in the methods of teaching which contributed much to the evolution of the school as we have it at present.

Hence, when Miss Nutting decided to accept the call to the Chair of Institutional Management in Columbia University, it was generally recognized that the training school had lost a most valuable officer, whose place would be filled with great difficulty.

The best wishes of the trustees, officers and pupils of the hospital and school for her success accompany her in her new field of labor.

It is gratifying to be able to add that Miss Georgina C. Ross has taken up the work which Miss Nutting laid down, and has prosecuted it with intelligence and vigor. She, like Miss Nutting, had been connected with the school for many years. She was trained here as a nurse, and after her graduation had filled many positions in connection with the school. As acting superintendent she has had charge of the school for several months, and has discharged a difficult range of duties with discretion, faithfulness and efficiency.

THE DEPARTMENT OF SOCIAL SERVICE

Dr. Hurd in this report referred at length to the social service department which had just been inaugurated.

It has long been evident that the work of the hospital, both in its wards and in the various out-patient services, has been incomplete by reason of the limitation of the sphere of physicians and nurses, who, from the nature of their connection with patients, necessarily confine themselves to the treatment and care of their physical ailments only. When the care of the hospital is withdrawn and the patients return to their homes, they frequently lose the benefit which they receive, because of bad social conditions, lack of proper food and improper hygienic surroundings. With the hope of relieving many of these conditions and helping to render permanent the good received while under treatment, the trustees of the hospital, largely through the initiative of Mr. John M. Glenn, one of their number, for many years closely identified with the public and private charities of Baltimore, have established a department of social service under the special charge of Miss Helen B. Pendleton, for many years a trusted and efficient agent of the Charity Organization Society of Baltimore. It is her duty to look after those persons who need something more than medical advice and prescriptions, and to bring them into relation with such charitable agencies or philanthropic persons as will enable them to improve their former unfavorable conditions of life. She has in her work the advice and council of Dr. Charles P. Emerson, who has for several years organized and directed a very extensive friendly visiting work among the poor of East Baltimore, and the assistance and active coöperation of a large number of friendly visitors from among the medical students of The Johns Hopkins University and other charitable workers.

The work under Miss Pendleton is still in its infancy, having been fully inaugurated only in September last, but its success already has been gratifying and encouraging. A kindred but less comprehensive work on the part of the officers of the hospital and the medical students of the university, as before intimated, had been carried on under Dr. Emerson's efficient and wise direction during the past five years.

1908

(February 1, 1908—January 31, 1909)

THE PHIPPS PSYCHIATRIC CLINIC

Dr. Hurd's report for the year ending January 31, 1909, speaks of the Phipps Psychiatric Clinic.

The Phipps Psychiatric Clinic, which was given by Mr. Henry Phipps last June, will soon be begun, and arrangements for the conduct of this department upon the completion of the building have been satisfactorily settled. The architect, Mr. Grosvenor Attebury, of New York, has the working plans well under way.

This is the most important gift that the hospital has received since its original foundation, and one which will undoubtedly add much to its usefulness. It is a matter of great satisfaction that we have been able to secure Dr. Adolf Meyer, of New York, as director, a man who in knowledge and experience ranks with the first men in the United States and Europe in his special calling.

The superintendent's report for the year ending January 31, 1909, contains three reports of exceptional merit—Report of the Phipps Dispensary Nurse; Report of the Phipps Dispensary, and the First Annual Report of the Social Service Department. These clearly show how much the hospital is doing for the welfare of the citizens of Baltimore in their own homes.

1909

(February 1, 1909—January 31, 1910)

In the report for the year ending January 31, 1910, is a splendid record of the work done by the new social service department.

To Dr. Henry M. Hurd, Superintendent of The Johns Hopkins Hospital:

SIR—The second year of the social service department ending February, 1910, shows a decided growth in the work. There are now 980 cases recorded as compared with 414 in the preceding year. . . .

That the hospital physicians recognize the usefulness of this department is shown by the increase in the number of cases referred to us from the wards. During the first year there were 48 cases, this year there have been 123. . . .

MARGARET P. BROWN,

*In charge of
social service department.*

1910

(February 1, 1910—January 31, 1911)

Dr. Hurd's report for the year ending January 31, 1911, refers to the resignation of Miss Ross, the superintendent of nurses and the appointment of her successor:

At the beginning of the fiscal year Miss Ross, in consequence of ill health, resigned her position and Miss E. M. Lawler was appointed superintendent of nurses and principal of the training school in her place. Miss Ross had been connected with the hospital since her graduation in 1894, and had served faithfully in many capacities in nursing service. She devoted herself assiduously to her work, and her failure in health was much deplored by all connected with the hospital. Her successor, Miss Lawler, is also a graduate of the training school, and for a time was assistant superintendent. Later she held responsible positions in connection with hospitals at Toronto, Ontario, Niagara Falls, N. Y., and Pittsburgh. Her training has been varied, her opportunities for acquiring familiarity with the duties of superintendent have been unusual, and she consequently comes to us an expert teacher. She has now given nearly a year's faithful service to the hospital, and her success gives every prospect of continued and increasing usefulness.

THE PROFESSOR OF PSYCHIATRY

In this report Dr. Hurd also referred to the development of the psychiatric department and to its director who had recently joined The Johns Hopkins Hospital staff:

The professor of psychiatry, Dr. Adolf Meyer, has been appointed psychiatrist to the hospital, and although the psychiatric clinic is not ready for occupation, Dr. Meyer has been able to do

very effective work in connection with the hospital wards and the out-patient department. It seems fortunate that prior to the opening of the Phipps Psychiatric Clinic it has been possible to utilize his services in connection with various charitable agencies in Baltimore. There is reason to anticipate when the clinic is opened that these relations may be productive of great good by promoting cooperation with the clinic on the part of many charitable organizations.

In the report for 1910 Dr. Hurd gave a complete list of the large gifts made from the opening of the hospital in 1889 up to the end of 1910.

1911

(February 1, 1911—January 31, 1912)

THE RESIGNATION OF DR. HURD

In the 23d report of The Johns Hopkins Hospital for the year ending January 31, 1912, on the page headed "Trustees" we find: President, Henry D. Harlan; vice-president, William A. Marburg; treasurer, John C. Thomas; secretary, Henry M. Hurd, M. D. On scanning the report still further we read [page 27]:

In May, 1911, Dr. Henry M. Hurd resigned from the superintendency of the hospital to become secretary of the board of Trustees, and Dr. Winford H. Smith, general medical superintendent of Bellevue and Allied Hospitals, in New York, was appointed his successor.

Dr. Hurd was the first superintendent of the hospital, and held the office for 22 years. Dr. Hurd's wise administration, his high ideals, his example and his readiness at all times to give of his knowledge to others, have contributed largely to the general development of hospitals throughout the country.

The man of small calibre is prone to pick out as his successor one who has even less ability than he possesses—one who by contrast will compare unfavorably with him. The man of vision, on the other hand, is anxious to have the work that he has carried on so successfully continue to broaden out and will suggest for the post he is relinquishing the best available man. Dr. Hurd with his usual good judgment of men recommended the best man he could find. The wisdom of his choice has been continually evident and it has ever been a delight to see how happy and how proud Dr. Hurd has been of the well-merited success of his successor, Dr. Winford H. Smith. Dr. Hurd's pride has been akin to that of a father who views with the greatest satisfaction the splendid achievements of his son; the more he accomplishes and the greater recognition his work receives the happier he is.

DR. HURD IN HIS RELATION TO THE HOSPITAL STAFF

When The Johns Hopkins Hospital opened there was no medical school from which to draw hospital interns and they consequently were continually recruited from all parts of the United States and Canada. This system had its advantages. Nearly every man came from a different school. The men compared notes, told one another of the methods in vogue in the school or hospital from which they had come, and thus each man soon became fairly familiar with what was being done in a medical way all over the country.

Some of these interns had had several years' training or by instinct immediately dropped into line. There were others of us who were young and immature and who needed careful and persistent training. Dr. Hurd was a past master in stimulating the house men to do their best. He did not molly-coddle them in the least. This good old state of Maryland is celebrated for its Maryland or beaten biscuits and it is a well-known fact that the more they are hammered in the making the better they are. Dr. Hurd with his keen perception soon learned this fact and he applied the principle to good purpose in his training of these men.* By a gentle but firm hint here and a rather emphatic suggestion there he soon transformed the raw recruit into a splendid house officer. Some of the men in the beginning hardly knew just how to take this discipline, but in a short time all thoroughly appre-

* I had often heard of an interesting interview the superintendent had with an incoming group of interns and also vague accounts of a very apt story related by the director on that occasion. I asked Dr. Hurd if he would mind repeating it. Here it is:

"THAT STORY"

"When the men who had been selected for the positions of interns at The Johns Hopkins Hospital out of the first graduating class of The Johns Hopkins Medical School came on duty, they found an organization for their work which had already been in successful operation for about eight years. They were bright enterprising students who were peculiarly receptive to all new ideas and much inclined to adopt them with little regard to their bearing upon the former routine of hospital service. As all were men of marked ability, some of the innovations which they wished to inaugurate were improvements without doubt and made for better service, but the general effect of their combined action caused confusion and a lack of co-ordination in the different departments. In fact, since the changes of hours of duty and general methods of work caused so much trouble, it was felt that some steps were needed to check a similar individualism on the part of equally active and zealous young men who were to enter hospital service in succeeding years. After the interns for the coming year had been appointed I called them into my office for a friendly talk about their duties and without referring to the embarrassments of the past year I rehearsed the tale of the small boy who while on his way to school trudging through the deep snow was overtaken by a gentleman, in a fine turnout with a dashing span of horses, who kindly asked him to ride with him. The invitation was joyfully accepted and the boy was soon making fine progress when the idea occurred to him that the driver of the horses was not driving them properly. He knew that he could drive them much better and suggested a transfer of the reins to him in order that he might display his superior skill. To his great surprise and discomfort his host stopped his sleigh and gravely but decidedly informed him that an invitation to ride did not carry with it the privilege of driving and that he might get out if he thought otherwise. I added that it gave the management of the hospital much pleasure to know that they were willing to ride with us during the coming year and I felt sure that such a journey together would be of great service to them and to the hospital, but I deemed it my duty to say frankly that the management of the hospital must do the driving and would continue to do so in future as it had in the past.

"The parable was promptly and correctly interpreted and there was never any difficulty in this respect with the interns at the hospital. They have always been loyal and co-operative in measures calculated to add to the efficiency of the hospital."

ciated the value of the standards set by the superintendent, and they would, later on, view with amusement and pleasure the probationary period of those who came after them. One and all soon came to realize that Dr. Hurd was their best friend. Many a time when one of the interns was in deep water—when illness occurred at home and he was called suddenly away, some one would quietly slip up beside him, place his hand on his shoulder and casually say "Can't I do something for you?" "Don't you need some money?"—many a man has had his load greatly lessened by this quiet, unostentatious friend.

A former student recently told me that toward the close of his second year he had reached the end of his resources and was preparing to leave the medical school and go to work.

Just after he had packed up and was arranging to leave that night Dr. Hurd met him in the hall and said, "By-the-way, I have been wanting to ask you how your father's estate has turned out," and the young chap told him the facts. Dr. Hurd took him into his private office, told him he must under no circumstances give up his studies and insisted on furnishing him with sufficient funds to see him through to the end of the college year, and next year saw that it was possible for him to continue his studies. This young man is now one of the most promising investigators in this country. He told me that he knew of at least five or six other students who had also been helped out by the same genial superintendent.

Dr. Hurd did not hold himself aloof from the house staff, but after the evening meal often dropped into the reading room to have a chat with the men congregated there. Every now and then an informal invitation came to dine with Dr. Hurd, Mrs. Hurd and his daughters. These were red letter occasions—events never to be forgotten.

Every one of the men who was connected with the hospital during Dr. Hurd's time has a vivid recollection of that tall, slender figure passing silently down the corridors with his head bent slightly forward and apparently walking on air, his tread was so light. He rarely was content to mount the stairs one step at a time, he invariably went up two at a time with his arms outstretched as if he contemplated an aerial flight.

Celebrated men who are closely associated with large numbers of young men are often given a special name as a mark of the esteem and affection in which they are held. When the men of the hospital staff of 20 years ago gather together and discuss old times they always refer to "Uncle Hank" with the warmest regard.

The visitor to the hospital—the one who comes to stay a few weeks or months—while impressed by the good work done in the various departments and by the original articles published by the hospital is more impressed by the spirit of coöperation and good fellowship that exists in the hospital and medical school. Dr. Hurd and the "Big Four"—Drs. Osler, Halsted, Kelly and Welch—have in large measure been responsible for this delightful atmosphere.

Many of the senior members of the hospital staff have been geniuses and it is a well-known fact that geniuses frequently become so engrossed in their individual subject that they are temporarily totally oblivious to the fact that other people have

to be considered and that these people have precisely the same rights and privileges as they. A tactful, gentle but firm tug emanating from the superintendent's office would awaken such an individual from his reverie. It was this absolute fairness on the part of Dr. Hurd that won for him the confidence and affection of the senior staff. They knew that they would always get a square deal.

Dr. Hurd's relations to the trustees have always been most pleasant. The trustees in their selection of the first superintendent looked the field over for the most able hospital executive they could find, and, when they had selected Dr. Hurd and he had accepted, they wisely abided by his mature judgment on all medical matters, and when he felt that it was wise for him to relinquish the exacting duties as superintendent of the hospital they insisted that he retain a connection with the institution and made him secretary of the Board of Trustees.

As we look back, it does seem a pity that Dr. Hurd did not have an assistant to relieve him of the many time-consuming and incidental details connected with his office. It was not until the last few years of his life in the hospital that he was relieved of these by the appointment of the late Dr. Rupert Norton as assistant superintendent.

Dr. Hurd was an ideal superintendent. In addition to the satisfactory administration of the hospital he was deeply interested in the fundamental education of the medical student and of the nurse. He was continually stimulating the house officers to do their best and was ever mindful of the welfare of the patient. He was no bureaucrat, but a man who had the interest of all connected with him at heart.

ARTICLES PUBLISHED BY DR. HURD WHILE SUPERINTENDENT OF THE JOHNS HOPKINS HOSPITAL

Most men after caring for the many details of such a large institution as The Johns Hopkins Hospital and editing the *BULLETIN* and *Reports* would find little or no time for other labors; not so with Dr. Hurd. With the indomitable energy which has always been so characteristic of him he kept right on with his literary work, each year writing one or more articles. His papers have in large measure been limited to four main subjects—psychiatry, hospital management, medical education and the education of the nurse.

In 1890 we find in the *Maryland Medical Journal* a paper on "Periodicity in Melancholia." Dr. Hurd in the same year was chairman of the Committee on Hospitals for the United States and made his report at the National Conference of Charities and Corrections held in Baltimore, May, 1890. Immediately after reading this report he addressed the assemblage on "The Relation of the General Hospital to the Medical Profession." In this address he clearly outlined what the general hospital should stand for. His ideas for that period were so advanced that I quote them.

The mission of the general hospital may be summarized to be: (1) To furnish medical treatment and proper nursing to the sick poor, and especially to the homeless and friendless; (2) to furnish similar treatment to those who are able and willing to

pay for it, and especially to those who are without families and homes; (3) to provide aseptic operating rooms where antiseptic surgery may be done with full confidence in its results—this confidence being based upon the knowledge that all scientific requirements have been met by proper construction and thorough management; (4) to provide instruction in and full demonstrations of the most approved methods of treatment of the sick to medical students and medical men; (5) to train capable, high-minded, self-sacrificing women as nurses; and finally (6) to advance medical study and increase medical knowledge.

It is evident that the old-time idea that the hospital is designed for the destitute and homeless alone must be materially modified to meet the present exigencies of modern life. Many persons in moderate circumstances live comfortably as long as they can labor and produce, but, when ill, can procure skilled medical attendance and proper nursing only at the cost of future debt and a weary struggle to pay the obligations incurred. The expenses of living are constantly increasing [1890] and the competition of modern life is intense, so that the majority of laboring men, of necessity, spend their earnings as they receive them, with little prospect of laying up a reserve for the traditional "rainy day." Hence, whether it be considered a good policy or not, provision must be made to care for many of these wage-earners in public hospitals in the event of long continued or serious illness. The same is true of the more wealthy classes. Many of them cannot procure at home the constant medical care and the thorough nursing required, and certain portions of the public hospital must be set apart for them.

In the *Transactions* of the Medical and Chirurgical Faculty of Maryland for 1891 appears a memoir to the late Richard Gundry, a well-known asylum superintendent and later a member of the Faculty of the College of Physicians and Surgeons of Baltimore. Dr. Gundry was an old and valued friend of Dr. Hurd.

In the *American Journal of Insanity* for 1892 Dr. Hurd published an article on "Journal Clubs." In this paper he spoke most enthusiastically of the value of such clubs and pointed out how they should be conducted:

For the success of a journal club it is essential:

1. That the work be made obligatory. It will not do to rely upon a zeal for study which may be cooled by other duties or by social obligations. The work should be made a part of the regular routine of the institution, and should not be pushed aside by any trivial matter. The same rule which governs excuses from any regular professional duty should govern all absences from the journal club. No new man should be added to the staff who does not intend to devote himself as loyally to this as to any other hospital or asylum duty. If outsiders are admitted—and I should say the more the better—they should come into the work under the same conditions.
2. A definite hour which will be reasonably sure to be free from interruption should be selected, and rigidly adhered to. Such an hour ought not to be at the close of an exhausting day's work.
3. The proceedings should be informal, and free discussion should be expected. The journal study should have the widest possible range. French, German and Italian journals should all be laid under contribution.
4. The work should be thoroughly supervised by the superintendent or some person whom he may select. Whoever takes charge of the club ought specially to prepare himself to sum up each subject and to present its practical bearings upon the better study or the better treatment of insanity. This will often involve

study and extra exertion; but such mental effort is recreative, and a grateful change from routine work.

The advantages of a journal club are manifold. A few of them may be mentioned:

1. It develops a spirit of professional study among the members of the hospital or asylum staff. The spirit of investigation and inquiry is easily lost unless special efforts are made to develop it. This is especially true where routine duties constantly press themselves upon the attention. Unless a spirit of study and inquiry is sedulously cultivated among the younger members of a medical staff, the zeal for professional advancement speedily disappears.

2. It provides for the systematic acquisition of knowledge by a division of labor; and the least possible waste of time on the part of each person concerned. This is an age of coöperation in literary work. Library and subject catalogues are undertaken by associated laborers; and enterprises which would be impossible to an individual become practicable to the many. Witness the success of H. H. Bancroft's gigantic historical enterprises. The work which he has finished by the aid of collaborators would have consumed 400 years of individual effort, had such a length of years been granted to the head of the undertaking. It is in keeping with the spirit of modern study to economize time and effort by multiplying workers. Psychiatry and neurology are so vast that each student cannot read the good, the bad and the indifferent. The grain should be winnowed before it is gathered into storehouses.

3. It supplies a common field of study where the members of the staff may meet for contact of mind with mind. By means of it, individual tastes and aptitudes for study may be utilized for the common good. It gives a broader professional aspect to asylum work by bringing each member of the staff into relation with the whole field of psychiatry. It also effects the readier training and more speedy assimilation of new members of the staff. Young men come to asylum work fresh from medical schools and hospitals with a keen zest for scientific work. This should be utilized, and habits of regular study in lines of psychical research should be acquired as speedily as practicable. The journal club will also contribute materially to the unification of a staff which may have been brought together from different schools of medicine. This is too often neglected in large asylums.

In 1892 Dr. Hurd published an article on "Post-Febrile Insanity." After discussing the subject in detail he recorded three cases of this character that had occurred in The Johns Hopkins Hospital, one after laparotomy for removal of diseased ovaries, one following pneumonia and a third during convalescence from typhoid fever.

In 1893 we find an article entitled "The Relation of Hospitals to Medical Education." This appeared in the *Boston Medical and Surgical Journal*, cxxix, p. 141.

In the medical writings of a physician one rarely has the opportunity of catching a glimpse of the personal charm or of the depth of sympathy of the writer. On October 14, 1894, a meeting was held in memory of the late George Huntington Williams, professor of geology in The Johns Hopkins University. Dr. Hurd had known him since he was a boy and was closely related to him by family ties. Dr. Hurd's tribute to his deceased friend brought out vividly that personal charm and sympathy which has always so endeared him to those with whom he has been closely associated.

In 1894 Dr. Hurd published a lengthy article on "Some Mental Disorders of Childhood and Youth," and in the *Bul-*

letin of the American Academy of Medicine, 1895-6, an article on "Laboratories and Hospital Work."

In the *Maryland Medical Journal* for 1896 we find a second article on "Paranoia."

In the *American Journal of Insanity* for 1895-6, p. 477, Dr. Hurd says:

It has been the custom of the *Journal of Insanity* during more than half a century to publish full details of new institutions erected for the better care and treatment of the insane; hence the recent opening of the new McLean Hospital at Waverly, near Boston, calls for more than a passing notice.

Dr. Hurd then describes in a most interesting manner this large institution for the care of the insane. He also gives illustrations and plans of the various buildings. The paper is a most complete one, occupying 26 pages.

On February 17, 1897, Dr. Hurd gave an address on "Hospital Organization and Management" before the Training School for Nurses at the hospital of the University of Pennsylvania. This was published in the *University Medical Magazine*, ix, p. 488. It contains much of interest and I quote some of the remarks made by Dr. Hurd on that occasion.

I cannot resist the temptation to say a word respecting the improvements which have been made in hospital construction during the past 30 years. These improvements I believe to be largely due to the experience of the Crimean War in Europe and of the Civil War in America. The first gave us training schools for nurses and trained nurses, and the latter improved hospital construction. These waves of progress from the East and West crossed the ocean in turn and brought to the whole world better facilities for the care of the sick and better methods of treatment.

The most noteworthy improvement in hospital construction has been in the direction of better sites for buildings, which are no longer crowded into narrow, dingy streets with unpleasant surroundings, and amidst insalubrious and unsanitary conditions, but are placed in open squares, in commanding situations, where sunlight and fresh air can freely come upon their joyous and health-giving missions.

The buildings themselves are more scattered, and sickness and suffering are diluted by differentiation and segregation rather than concentrated by piling one ward upon another. Hospital wards also have been more conveniently arranged to do their appointed work, and have had comforts and conveniences in the way of service-rooms, tea-kitchens, rooms for the dangerously ill and dying, and the like, which have contributed immeasurably to the comfort of the sick. Special efforts have been made in the construction of wards to provide for heating, ventilation, the isolation of infectious, harmful, or offensive patients, and for all sanitary needs. Laboratories for the investigation of disease have also been built and fitted with instruments of precision for the more accurate and scientific study of disease processes. Operating rooms have been planned and erected at lavish expense to carry out as strictly as in a laboratory all the requirements of antiseptic surgery. Disinfecting plants have been joined to every hospital to destroy the germs of disease and to prevent the transmission of infection from one patient to another.

It is related that a surgeon-general of the United States Army, now deceased, once stated that it was no part of the work of the army medical corps to study disease or to engage in any work of research, but rather to cure sick soldiers, forgetting that the cure of sick soldiers is more promoted by the spirit which leads to the study of disease than by the narrow view that the indi-

vidual soldier at morning sick-call alone should engross the attention of the army surgeon.

The best method of keeping the torch of knowledge lighted is to pass it along from hand to hand. Hence I have little sympathy with those who deplore the use of hospital wards as means of instruction. They should be used for the training of nurses and for the instruction of medical students, and by their very use for these purposes their efficiency for the cure of disease will be augmented.

In a well-ordered hospital, as in a well-ordered state, there should be an ultimate and final authority, a proper subdivision of duty, and a thorough adjustment of all portions of a complex and often cumbrous mechanism to its special uses. It is the part of a Board of Trustees to establish the policy of the hospital, to give an impetus to the machinery, to oil and readjust it from time to time, to watch its operations, and to scrutinize its results.

A friend of mine used to say that responsibility without power is weakness. Responsibility and authority must go hand in hand.

If I were asked to indicate the best machinery for hospital government, I should say a Board of Trustees to be sovereign and responsible for the whole institution, a medical board to advise the trustees in all medical matters, a chief executive officer to be known as director, secretary, or superintendent, whose duty it should be to coördinate and supervise all other departments, a purveyor to look after food-supplies, a matron to supervise the household and a superintendent of nurses to have charge of the training school and the nurses. Under these heads of departments there should be subordinate chiefs of departments, like the engineer, chief cook, laundry man, diet-school teacher, store-keeper and the like.

A word as to discipline. From the character of the work of a hospital and the necessity of the development of kindly instincts and humane methods of thought and action among all employés, it is unwise to establish and enforce a semi-military discipline or even one which would be practicable or advisable in a railway, a large factory, a corporation, or other business enterprise. There should be a rigid discipline and a strict accountability for the performance or neglect of duty, but this discipline should be sustaining in its nature and calculated to develop the individual. Through its kindly control the thoughtless or untrained nurse or employé should be lead to a higher level of conduct and feeling until her better nature becomes the governing power. To many hospital employés the life becomes truly educational, and the officer who does not strive to make it so falls of an important duty. A wisely directed enthusiasm, a kindling of the moral nature, a glimpse of a higher, broader, and more satisfying life can thus be given to all who have to do with the sick in the hospitals. Hospital work, when done with loving, eager enthusiasm, blesses the patient and the nurse alike. It should be the aim of all to do charitable work in a charitable, kindly way. I have little patience with those who look upon the medical treatment of the sick in hospitals as a business matter only, and the nursing of the sick as an avocation, a trade, a preparation for getting a living, a matter of hours on duty to be endured as patiently as possible for the relief which is afforded by getting through with them. Unless the care of the sick can be glorified by sympathy, kindly feeling, enthusiasm and personal interest it becomes drudgery and heartless routine. Hence the necessity of developing the best instincts of all who have to do with the sick by a sustaining, fostering and kind discipline which regards the individual and not the mass.

Much of the alleged lack of sympathy sometimes complained of on the part of the hospital physicians, nurses and employés, I believe to be due to overwork.

In 1897 Dr. Hurd and Dr. John B. Chapin, physician-in-chief and superintendent of the department for the insane of

the Pennsylvania Hospital of Philadelphia, Pa., were asked by the "Joint Select Committee to Investigate the Charities and Reformatory Institutions in the District of Columbia" to make a report on the hospitals of the District of Columbia. This they did and their findings were embodied in a paper presented to the committee on November 24, 1897. This report embraced a full description of the Asylum and Almshouse Hospital; the Children's Hospital; the Columbia Hospital for Women and Lying-in Asylum; the Central Dispensary and Emergency Hospital; the Freedman's Hospital; the Garfield Memorial Hospital; the National Homœopathic Hospital and the Home for Incurables. The report is an exhaustive one. It points out the excellent features in each institution, draws attention to the weak spots, and makes numerous admirable recommendations looking to the more systematic and the better handling of patients in the District of Columbia.

In the *Albany Medical Annals* for February, 1898, we find an article entitled "The Medical Service of Hospitals," and in the *Maryland Medical Journal* for 1898-9 Dr. Hurd considers "The Non-Medical Treatment of Epilepsy."

At a meeting of the Gynecological and Obstetrical Society of Baltimore, December 13, 1898, Dr. Hurd gave a paper on "Post-Operative Insanities and Undetected Tendencies to Mental Disease." This article appeared in the *American Journal of Obstetrics*, Vol. xxix, 1899. It is interesting to read Dr. Hurd's views on the subject. They are of much importance to the laity as well as to the surgeon.

Post-operative insanity may be considered a complex affair, comprising symptoms which may differ in cause, manifestation, course and termination. There would seem, in fact, to be little ground for the use of the term, were it not for the existence of infectious processes accompanied by delirium or prolonged depression. In other words, if an operation is free from septic infection in a case destitute of any tendency to insanity, there can be no ground to think that the operation *per se* produces mental disease or that the insanity is post-operative in the sense that the operation bears a causative relation to the insanity. There are disturbing factors, it is true, in connection with surgical operations, which may be competent to produce an insanity, and I will briefly refer to some of them; but the insanity which they produce can only be considered post-operative in point of sequence rather than of causation. It is unquestionable that the prolonged use of anesthetics like ether, chloroform, or nitrous oxide has produced excitement, delirium, mental confusion, and often prolonged mental alienation without the accompaniment of any operation whatever. Instances are also not at all uncommon where, following an operation, excitement has followed the local application of iodoform, the instillation of atropia or the administration of the salicylate of soda, and where, notwithstanding the surgical operation, the symptoms of insanity subsided wholly upon the withdrawal of the intoxicating agent.

Similarly, we may have mental symptoms following an operation clearly ascribable to shock, loss of blood, excessive exhaustion from the fatigue of a constrained and unnatural position, long-continued vomiting from an anæsthetic, or abstinence from food owing to anorexia. There may also be a poisoning of the blood and consequent interference with proper cerebation from defective action of the kidneys, due wholly to the withdrawal of water by the mouth lest it may excite vomiting after an abdominal operation; or the anæsthetic may have caused a transitory neph-

ritis with accompanying loss of kidney function. These and similar causes which are not surgical in character, but are necessarily an accompaniment of a surgical operation may produce insanity which cannot in any manner be differentiated from actual post-operative insanity due to infection.

In 1899 Dr. Hurd was president of the Medical Psychological Association. On that occasion he took as the theme for his address "The Teaching of Psychiatry." That his interest in the care of the insane never flagged is clearly shown by the fact that from the first meeting of this association in 1879 up to the time of his presidency in 1899 he had missed but two annual meetings.

In this address he paid a touching tribute to an old friend:

While engaged in writing this address the crushing news comes of the sudden death of Dr. Godding. It is difficult to realize that our noble-hearted and cultivated associate has gone from earth. He had a poet's soul, the charity of a saint and the heart of a child. He loved poetry, literature, art and music; above all, he loved his fellow-men.

In 1900 Dr. Hurd published a splendid article entitled "Hospitals, Dispensaries and Nursing." At the end of this paper he gave a list of the principal hospitals of the United States that had been established during the last century.

In the *Bulletin of the Iowa State Institution* for 1901 appears a paper by Dr. Hurd entitled "Reception Hospitals for Cases of Acute Insanity."

On November 21, 1901, Dr. Hurd delivered an address on "Psychiatry in the Twentieth Century," at the opening of an additional building at the New Jersey State Hospital at Morris Plains. After paying a tribute to the late Miss Dorothea L. Dix, whose work had been such a benefit to New Jersey as well as to the entire country, he sketched the gradual changes that had taken place in the treatment of the insane in the United States. He then pointed out where improvements might with profit be made in the handling of mental cases. The pith of his remarks is contained in his concluding paragraph:

The future of psychiatry in America is bright with hope. The era of foundation and construction is nearly over; institutions have been evolved, developed and perfected; pathological institutes have been established and liberally equipped and supported; trained men with broad learning and technical knowledge have been raised up for special study, and an earnest spirit of investigation has been developed. We are on the threshold of new discoveries and important improvements in the treatment of the insane.

In 1902 Dr. Hurd addressed the graduating class of the training school of the Garfield Hospital at Washington, D. C. He took as his theme "The Educated Nurse and Her Future Work." This paper was later published by the Friedenwald Press in Baltimore. It should be carefully read by every undergraduate and graduate nurse. It will also give to the lay reader a very clear idea of what real nursing means—it portrays in no uncertain terms how much the medical profession owes to the trained nurse.

Dr. Hurd gave a charming address on "The Duty and Responsibility of the University in Medical Education," at the graduating exercises in the Yale Medical School on June

23, 1903. After briefly considering the subject of his discourse he said:

To discuss an educational question before university men suggests the appropriateness of the quotation from Confucius with which an eminent scientist once prefaced an address made under similar circumstances: "Avoid the appearance of evil: do not stoop to tie your shoe in your neighbor's melon patch." A member of the teaching staff of one of the newest schools of medicine ought to display a degree of modesty in the presence of medical teachers whose thoughts and activities have been molded by the traditions of one of the oldest medical schools in the United States, the sixth in point of time of establishment, and should hesitate above all to urge the duty and responsibility of a university in medical education.

Perhaps I may also plead in mitigation of my indiscretion a degree of hereditary relationship to Yale in the fact that my father graduated here in medicine in 1830; my grandfather was a student about 1795, but did not graduate; my great-grandfather graduated in 1778; and my great-great-grandfather in 1739, and may speak as one whose speech can be tolerated because of kin, albeit remote.

In his remarks directed especially to the graduating class he said:

In your chosen profession be students and productive workers always. Do not look for speedy results and do not be discouraged if the secrets of nature are not wrested from her jealous grasp without a severe struggle. The foundations of our art are broad and deep, and the superstructure should be erected slowly and with care, by accurate observation of disease and painstaking deductions. In your life as physicians be prepared for trials, disappointments and adversities. Take for your motto the words written by Sir Thomas Browne, that eminent physician, more than two centuries ago: "In this virtuous voyage of thy life hull not about like the Ark without the use of Rudder, Mast or Sail and bound for no Port. Let not disappointment cause Despondency nor difficulty Despair. Think not that you are sailing from Lima to Manilla, when you may fasten up the Rudder and sleep before the Wind; but expect rough Seas, Flaws, and contrary Blasts; and 'tis well if by many cross Tacks and Veerings you arrive at the Port; for we sleep in Lyons Skins in our Progress unto Virtue and we slide not but climb unto it."

Have a purpose and carry it out with fortitude. There can be no more absorbing or inspiring career than is afforded by the study of medicine at the present time. The scaffolding reared by countless workers during thousands of years around the fair temple of medicine, necessary for the building doubtless, but concealing its proportions and too often defacing its beauties, has been swept away, and for the first time it is permitted to us to know something of the dimensions and architectural possibilities of the completed edifice. Can there be a nobler aspiration for any man than to assist in the completion of the work of transforming the ancient art of healing into the science of medicine?

In 1902 Dr. Hurd was the chairman of the Section on Neurology and Psychiatry of the Medical and Chirurgical Faculty of Maryland. At a meeting of the section held November 14, 1902, he took for his subject "The Future Policy of Maryland in the Care of Her Insane." When in Michigan he did not hesitate to tell the state just what her duty was in the care of the insane. In Baltimore he spoke out in the same fearless manner. He had carefully studied the situation in Baltimore and in the various counties. Maryland was far behind the times and at the meeting of the Medical

and Chirurgical Faculty in 1897 a symposium on the state care of the insane had been arranged. The papers read on that occasion brought forth much resentment on the part of the state authorities.

Dr. Hurd in his address in 1902 pointed out what had been accomplished in the interim, but also stated in no uncertain terms that in many places throughout the state the conditions were still deplorable. He did not generalize as is so frequently done, but was specific, mentioning the institutions at fault. He then indicated how these appalling conditions should be rectified.

A man who has the nerve and patriotism to come out boldly and draw attention to the glaring faults in his own state and at the same time to indicate the means by which these conditions can be ameliorated is without a doubt a most valuable man in his community—he is a real citizen.

Dr. Hurd's concluding paragraph addressed to the medical profession was peculiarly apt to the occasion:

Those who have read the recently published life of Pasteur (every physician ought to read it) must have been impressed by the fact that in the mind and life of this wonderful man scientific knowledge was invariably regarded as the hand-maiden of humanity. In the height of Pasteur's interest in the study of ferments, which opened the way to our present antiseptic surgical methods, he turned aside from his chosen work for five years to study the diseases of silk-worms, because of the sufferings of the people in certain portions of France consequent upon the destruction of the silk industry. His subsequent studies in puerperal fever, charbon, chicken cholera, plague and hydrophobia were inspired by a similar notion; to use his own words, "To give the heart its share in the progress of science." We may not be able to imitate Pasteur in scientific achievement and in broad and vivifying generalization from isolated scientific facts, but we can imitate his broad humanity and his desire to ameliorate the lot of the unfortunate. We can at present do no greater service to humanity and the commonwealth than to use our professional influence and personal effort to promote the hospital treatment of acute cases of insanity and appropriate state care for the insane poor of the chronic class.

All interested in the care of the insane should read this article in full. It appeared in the *Maryland Medical Journal*, February, 1903.

Thanks to Dr. Hurd and his colleagues the disgraceful condition that then existed has long since been corrected. The State Lunacy Commission, then more of an advisory board, now has ample authority and at the present time Dr. Hurd is the most valuable member of the commission.

In 1904 Dr. Hurd gave the address to the graduating class of the Training School for Nurses at the Albany Hospital. He took as his theme "Is Nursing a Profession?" This paper was published in the *Albany Medical Annals*, September, 1904.

In his address at the graduating exercises of the Lakeside Hospital School for Nurses in Cleveland, in 1906, his paper was entitled "Shall Training Schools for Nurses be Endowed?" This is a theme that is engrossing the attention of more than one institution.

In 1906 Dr. Hurd read a paper entitled "The Medical Organization of General Hospitals," before the eighth annual

meeting of the Association of Hospital Superintendents. This article was published in the *National Hospital Record* in October of that year. At the annual meeting of the Canadian Hospital Association, held in 1908, Dr. Hurd spoke on "The Proper Length of the Period of Training for Nurses." This paper was published in the *American Journal of Nursing* in June, 1908.

In May, 1908, Dr. Hurd gave a paper on "Psychiatry as a Part of Preventive Medicine." This was published in the *American Journal of Insanity*, 1908-9.

The object of preventive medicine being to lessen the burdens of mankind by obviating preventable diseases, it is deemed appropriate at this time to inquire in what manner the experience of those who are familiar with the problems of psychiatry may be utilized to assist in this good work. It needs no elaborate demonstration to show the evils of insanity and the heavy public and private burdens which it entails upon every community. Next to alcoholism it is probably the most potent cause of pauperism and dependence.

The article is a most instructive and important one. The conclusions are particularly interesting:

The methods of rendering the teachings of psychiatry more effective to prevent disease should be:

1. To instruct children in the schools the art of healthy and useful living. Teaching should be more thorough and not restricted to fit one to get on in the world, but rather to inculcate ideals which will give him a conception of the prime importance of self-control and moral rectitude. It should also include a knowledge of the dangers of immorality and intemperance.
2. To use the newspapers and the special reports of officers of institutions for the insane and defective classes, to scatter broad cast a knowledge of the laws of bodily and mental health, and the best means of preventing the development of mental disorders.
3. To give a better recognition of psychiatry in the curriculum of every medical school, so that physicians may become familiar with the diagnosis and treatment of insanity. To this end psychopathic hospitals should be established to give clinical instruction, so that the family physician may recognize insanity, may be able to scrutinize carefully the mental condition of neurotic children and may give wise advice upon all educational problems.

In the *Nursing Mirror* for 1908-9, Dr. Hurd published an important paper on "State Registration and the Education of Nurses in the United States."

On November 30, 1910, a Health Conference was held in Pittsburgh. On that occasion Dr. Hurd gave a short but most practical paper on "Coöperation Among Hospitals." In this address he emphasized the great value of coöperation. He said:

Hospitals are often established by too zealous friends for these medical men, or established hospitals fall under the dominion of two rivals in the profession. Under the circumstances, coöperation between the two hospitals becomes difficult and often impossible. I know many cities where such bitter feelings have in the past destroyed all hope of coöperation and where the friends of able physicians or surgeons formed two armed camps. Even the ladies become enlisted and fight under one or the other banner. I am glad to say, however, that the days of bitter rivalry between hospitals are passing away. The whole world is becoming more tolerant and the *odium medicum* is following the course of the *odium theologicum*. May its departure be as speedy.

In referring to the purchase of hospital supplies he mentioned a method that has given splendid results:

A very obvious form of coöperation is for all the hospitals of the city to adopt a common standard of ordinary every-day supplies and to arrange for their purchase through a common purchasing agent.

In the city of New York recently also an attempt has been made with very gratifying success to establish a hospital bureau, which is a central supply bureau under a purchasing agent, whose duty it is to make contracts for gauzes, cottons, surgical instruments, rubber goods, furniture, fixtures, bedding, blankets, linen and the like. These supplies are purchased in large quantities according to a definite standard of excellence and at the lowest market prices. The saving of expense in the cost of supplies is considerable, but the saving to the hospitals in the payment of salaries to the officers to purchase is probably equally great. The same is true of breadstuffs, fuel, machinery, etc. Every department of the New York hospitals has profited by the central bureau.

Hospital officers often do good in secret and the community at large does not appreciate how much is done by the unpaid and unselfish men and women who are managing our great hospitals. The good work they do should be better known and this can only be known by a wide publication of their work. They should not put their candle under a bushel, but on a candlestick, that all may see and coöperate in helping on their good work. There are hundreds of men and women who long to do good, but who need to be set at work. Tell the public what you are doing and do not hesitate to ask for substantial support.

At the graduating exercises of the Nurses' Training School of The Johns Hopkins Hospital on May 19, 1910, Dr. Hurd gave a delightful address on "Florence Nightingale—a Force in Medicine." He said:

I desire rather to speak of her career as a constructive philanthropist, as a sanitarian and as an organizer of nursing service in city and country, of her statesmanlike grasp of the problems of army nursing and of the influence of her life work upon the medicine and surgery of the past half century.

In the course of his address he refers to the visits the late Francis T. King, the late Mrs. Robb, and Miss Nutting had with Miss Nightingale. Dr. Hurd's address was most interesting from beginning to end. I shall quote a few paragraphs.

It is my task this afternoon to tell you in what manner she has influenced the wonderful progress of medicine during the past 50 years.

1. First, and probably to a larger degree, she has wrought for medical progress through her reform in nursing. She found it an occupation and has made it a calling. From the very beginning of her career she insisted that any woman who engaged in nursing should qualify herself as thoroughly for it as a man qualifies himself for any calling in which he expects to succeed. She believed that the object of training was to teach not only what was to be done, but how to do it. The physician or surgeon should order whatever needs to be done for the patient's care, but the training of the nurse should teach her how to do it to his order. Training, also, should teach the symptoms of disease, so that the nurse may know what certain symptoms indicate about any disease and whether the patient is worse or better when the symptoms change. Telling the nurse what to do is not enough and cannot be enough to make her work perfect.

2. In all her writings Miss Nightingale has constantly dwelt upon the value of sanitation and obedience to the laws of health. She speaks with endless iteration of the need of pure air, pure

water, efficient drainage, perfect cleanliness and sun-light in the sick room. . . .

Her books in fact have been an immense influence in promoting the sanitation of the home and of the public and private hospital. They furnished principles for the guidance of those who would work out their own plans, when principles had once been enunciated and detailed and specific plans for those to follow, who cannot plan for themselves. Her suggestions and directions for the care of patients in their own homes are invaluable and have never been equaled by any other writer. She cries aloud and spares not for good sanitation and for the care of the patient. She may not always be in accord with present theories of the bacterial origin of many diseases and may err in ascribing measles and other infectious diseases to a lack of sanitation, but her main thesis that bad air and all dirt are dangerous is unsailable. . . .

It may be called to mind that at this hospital its founder, Johns Hopkins, made provision equally for the care of the sick, the instruction of medical students and the training of nurses, each duty being equally obligatory. . . .

3. One of Florence Nightingale's most important contributions to medical progress is to be found in her "Notes on Matters Affecting the Health Efficiency and Hospital Administration of the British Army, Founded Chiefly on Experiences of the Late War." This work in my opinion constitutes one of the most valuable contributions ever made to hospital organization and administration in time of war. Had the conclusions which she reached been heeded in the Civil War in America or in the Boer War in South Africa or in the Spanish-American War, hundreds of thousands of lives might have been saved and millions of people might not have mourned over a useless and needless sacrifice of the flower of their young men. Her ability to analyze dry statistics and army returns and her rare power to draw correct conclusions from them seems remarkable.

Probably one of the most interesting articles that Dr. Hurd ever penned was entitled "The Site of the Johns Hopkins Hospital." This paper was read at The Johns Hopkins Hospital Historical Club in December, 1910, and published in the *Johns Hopkins Nurses Alumnae Magazine*, April, 1911.

A plat of the site of The Johns Hopkins Hospital which was prepared to facilitate the sale of the property to the late Johns Hopkins has recently come to light among the records of the hospital and an examination of the survey has suggested to me that it will be interesting to all persons connected with the hospital to see it and to learn something of its previous history.

The site of the hospital has been used for hospital purposes for somewhat over 100 years. A general hospital was established on this site in 1797 or in the early part of 1798. In an old report it is spoken of as a beautiful site upon a hill, about a mile from the city of Baltimore. When I came here 21 years ago, the town extended but a little to the east of the hospital and most of the neighboring streets have been opened since the present site was selected.

Dr. Hurd then sketches the early history of Baltimore in a most fascinating way and refers to the epidemic of yellow fever that invaded Baltimore. In 1808 the old hospital was leased to a firm of physicians, Drs. Smyth and Mackenzie. In 1834 it was used as a lunatic asylum, later called The Maryland Hospital for the Insane.

From Dr. Hurd's paper we learn that at one time the town of Joppa on the Gunpowder River was larger than Baltimore and that from this town there was a brisk trade in tobacco, many ships sailing from Joppa to England. The old Joppa

Road ran from Joppa through Baltimore to Annapolis. It crossed the present hospital ground a few feet north of the present administration building. A house that faced on the Joppa Road existed until a few weeks ago (June, 1919) and its front foundation can still be seen on the south side of Monument Street between Bond and Caroline streets. It was located directly behind the moving picture parlor frequented by colored people. This building was clearly visible from Monument Street when the picture parlor was being constructed. Judging from the front of the house the Joppa Road crossed the present Monument Street, going northward and westward between Bond and Caroline streets. In 1836 land was bought by the hospital on the north of the Joppa Road and this once busy main thoroughfare was closed.

Johns Hopkins died the day before Christmas, 1873, and early in the following February the trustees organized for the first time as a board and arranged to take over what property was ready for them. . . . They made an effort to get competitive plans, but finally gave it up and Dr. J. S. Billings, who is now at the head of the New York Public Library, went abroad with a set of plans which he submitted to all persons who were skilled in hospital construction. In 1874 the original buildings had been torn down, but it was not until 1876 that Dr. Billings returned with his plans. . . .

The buildings were begun in 1877, but were erected no faster than the trustees had the money to pay for them. They built them wholly out of income and when money was not available to continue the work they ceased building operations until more money came into the treasury. The result was a delay of full 12 years before the buildings were completed. The trustees were bitterly attacked by the newspapers, especially in the columns where the letters of the people appear, but they went on in their own way and when the buildings were completed and opened in 1889, they had been constructed wholly out of income and the capital fund of the hospital had been increased more than \$100,000 during the process of building. Many hospitals are built after a different plan and must contend with poverty and debt for many years. The trustees of The Johns Hopkins Hospital were more sensible. They knew that the hospital was to last for a long time and that there was no reason why they should cripple it for all time in order that it might be opened a few years sooner.

Dr. Hurd then gave a short account of Johns Hopkins's life. Accompanying the article is a picture of the old Maryland Hospital; the real estate plat of the present hospital area showing the position of the original Maryland Hospital on this ground and the location of the Joppa Road. The last picture shows the site of the present hospital—a broad fence around it, a tent on the site, and many men and horses, ready to begin the excavation for the foundation of The Johns Hopkins Hospital. Every one interested in the institution will be delighted with Dr. Hurd's article.

DR. HURD, SECRETARY OF THE BOARD OF TRUSTEES OF THE JOHNS HOPKINS HOSPITAL.

Shortly after Dr. Hurd relinquished his duties as superintendent of the hospital he moved "across town" to 1023 St. Paul Street where he has since resided. His secretarial duties have occupied much of his time, but he has nevertheless

always somehow made time for his literary work. The first article from his pen after he became secretary was "Early Days of The Johns Hopkins Hospital and Medical School." A perusal of this splendid historical sketch gives one a graphic picture of the hospital in its formative days. To one who was on the scene in those delightful days it brings back priceless memories. In order that the reader may recall some of the milestones I will quote sections of this sketch:

The late Johns Hopkins procured an act of incorporation of his future hospital from the Maryland Legislature in 1867 and named 12 able men, nearly all of them intimate and trusted friends or relatives, to act as incorporators and trustees. Beyond deeding to this Board of Trustees a site for the institution, which consisted of the buildings and grounds of the old Maryland Hospital for the Insane, founded in 1797, he had taken no further steps towards its erection at the time of his death in December, 1873. . . . The actual work of construction did not begin until 1877, and the hospital was not opened until 1889.

The medical school, for which Mr. Hopkins made provision in his will, when he made his bequest to the university, was not opened until 1893, 20 years subsequent to his death. These delays and disappointments were due to financial difficulties, for which the trustees of the university were in no way responsible. . . .

In August, 1889, when I came to Baltimore to assume charge of the hospital as superintendent, I found four wards in commission, *viz.* a pay ward for men and women, two public wards for men and a public ward for women. An out-patient department had also been opened under the charge of Dr. Halsted. The pathological laboratory, under the charge of Dr. Welch with a corps of assistants, had been operated as a branch of the university since 1886, although recently under the joint control of the hospital and the university, owing to the financial difficulties which hampered the university at that time.

Dr. W. H. Welch was in the full tide of his brilliant career as a teacher, and had attracted to Baltimore such men as the late Christian A. Herter and W. S. Halsted, of New York, W. T. Councilman, now of Harvard, A. C. Abbott now of the University of Pennsylvania, F. P. Mall, later at Clark University and the University of Chicago, and many others of equal prominence, who were all deeply engaged in medical research. Possessing encyclopedic knowledge, unusual geniality and large-mindedness in his relations with other men, and the gift of exposition, so essential to the true teacher, he has been an active factor in the university and hospital for many years. He is above all an investigator with a judicial cast of mind and with the ability to stimulate his associates and students to productive work, and the greater ability to exercise a wise control over them.

Dr. W. S. Halsted was at the head of the surgical work of the infant hospital which he had organized in accordance with the newer teachings of Lord Lister, along the line of a better technique based upon the teachings of bacteriology. He possesses the faculty of constructive work not alone in the principles of surgery, but also in the details and minutiae of surgical technique. He is eminently thorough in all that he undertakes to do and whatever principles of surgery he has established have been firmly founded upon experience as a surgeon, diligence as an investigator and experimental studies upon the lower animals. He was then beginning to develop what was to become during the next 20 years a school of surgery, not only in what was accomplished, but also in the influence which he exerted upon new men and the training which they received.

Dr. William Osler had lately come from Philadelphia as physician-in-chief of the hospital and had already attracted much

attention by reason of his unique personality, his versatility in medicine and his literary facility. He was a master of English, deeply versed in the history of medicine, an expert pathologist, a well-trained diagnostician, filled with knowledge of practical medicine, and a remarkable clinical teacher. He had unwearied industry and a wonderful ability to utilize his gifts to accomplish beneficial results for medical science and for the world. His call to Oxford in 1905 was a serious blow to the hospital.

It is remarkable that three such men as Welch, Halsted and Osler should have been found to launch the hospital on its successful career, each possessing different powers and yet all working harmoniously to supplement the activities of each other.

In October Dr. H. A. Kelly, came from Philadelphia to assume his duties as gynecologist-in-chief of the hospital, and established a public and private ward for surgical diseases of women. He was and is a brilliant operator whose mechanical deftness and manual skill have been the admiration, envy and despair of all who have followed his work in the operating room. His ability to devise new operations and to meet emergencies in surgery is phenomenal. In addition to an extensive surgical work he early became interested in the preparation of surgical books which were clearly written and beautifully illustrated by the best medical artists procurable in this country or Europe. His interest in art as applied to medicine and surgery has been an important contribution to the profession and has influenced widely medical literature in America. Equally with Osler, Welch and Halsted, he has trained students to do excellent work as operators and teachers throughout the country.

All of these leaders were young men, the eldest not being more than 40 years of age and many of them much younger. Gray hairs thus far have not adorned the heads of most of those who were interested in the development of the hospital, although it must be acknowledged that some might have grown gray if they had retained their original covering. All were wisely interested in the public welfare and used their influence in the city, state and country at large to improve sanitation, to give better care to the poor, earlier help to the tuberculous and to institute healthier conditions of living generally. . . .

In the *Journal of the American Medical Association*, 1912, Vol. lix, p. 1677, Dr. Hurd published a paper on "The Proper Division of the Services of the Hospital."

In 1912 he was president of the fourteenth annual meeting of the American Hospital Association. He took for his theme on this occasion "Hospital Problems." This address appeared in the *International Hospital Record* for that year.

In the *Bulletin of the Medical and Chirurgical Faculty of Maryland* for 1912-3 he published an interesting paper entitled "Extracts from the Laws of Maryland and Virginia Regarding the Early Care of the Insane."

Dr. Hurd's paper "Three-Quarters of a Century of Institutional Care of the Insane in the United States" appeared in the *American Journal of Insanity*, 1912-3, Vol. lxi, p. 469. He divided the care of the insane during this period into four stages:

1. The period of neglect.
2. The era of awakening.
3. The period of state care of the insane.
4. The period of scientific care.

After considering each of these stages in detail he took up: Laws for commitment of the insane in every state; the criminal insane; detention hospitals; hospitals for the chronic insane; after-care of the insane; architectural changes and improve-

ments; scientific work; biographies, etc. The article is a very instructive one even for those who know little about psychiatry.

In the *Modern Hospital* for 1913 we find two articles from Dr. Hurd's pen, "The Hospital as a Factor in Modern Society" and "Hospitals and the Reform of Medical Teaching."

During the year 1914 Dr. Hurd contributed eight papers to the literature, "Some of the Writings of the Late Eugene Fauntleroy Cordell"; "Relation of the General Hospital to the Training School for Nurses"; "Hospital Medical Statistics"; "The Small Hospital a Factor in Medical Education"; "Mental Cases in General Hospitals"; "The Human Side of Florence Nightingale"; "Rupert Norton"; "State Registration of Nurses."

Dr. Cordell was the medical historian of the University of Maryland and had published a most valuable history of medicine in Maryland. His book is a very interesting one and will long remain the source of information relative to medical events in this state.

Dr. Rupert Norton had been associated with Dr. Hurd for several years. He remained assistant superintendent when Dr. Winford H. Smith succeeded Dr. Hurd. In 1914 Dr. Norton developed typhoid fever and died.

Dr. Hurd in his article paid a well-deserved tribute to his former associate.

A reference to Dr. Hurd's bibliography shows that he published no less than eight papers in 1915. Among them were "The Early Years of The Johns Hopkins Hospital"; "Forty-Five Years Ago and Now"; "The Treatment of Mental Cases in General Hospitals"; "The General Government of State Hospitals."

In 1916 Dr. Hurd in addition to a tremendous amount of editorial work he had under way published six papers. They were "Some Sources of Friction in the Management of Hospitals"; "Another Source of Friction in Hospital Administration"; "Who Shall Manage the Training School for Nurses?"; "The Advantages of the Budget System"; "Nathan Smith, Nathan R. Smith, and Alan P. Smith—a Medical Family"; "Need of Segregation of Imbecile Women."

On March 12, 1917, Dr. Hurd read a paper on "Johns Hopkins and Some of His Contemporaries" before the Historical Club. This was published in the July number of the BULLETIN for the same year. In his introductory remarks Dr. Hurd says:

The primary object of our Historical Club, when it was founded, was the study of medical history. To-night I have thought it wise to speak of the life of one who was not directly connected with the history of medicine, but who, because of the influence which the university and hospital he established have had upon medical education in this country, seems closely allied to medicine. I have also an additional reason for speaking briefly of his personal history before this club, because as the years pass I find that the career of Johns Hopkins becomes less familiar to the present generation, and there is danger that he may become a mythical personality. This is my reason for speaking of his origin and personal characteristics and giving some account of his career in Baltimore. I also wish to speak of his personal interest



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Henry M. Hurd

in the hospital and of the men he selected to carry out the enterprises.

Dr. Hurd then briefly sketched the life of the founder of The Johns Hopkins Hospital and also gave a short account of the original trustees of the hospital.

With a record of so much work done after resigning the superintendency the reader will naturally ask why Dr. Hurd did not remain at the helm. Physically, mentally and in every way he was still in his heyday, but he felt that he had borne the heat of the day long enough and that the running of the hospital should now be placed in younger hands. One of the trustees of the hospital who spent several weeks traveling with Dr. Hurd some years after he had retired from the superintendency was so much surprised at his agility that he turned to me and said, "I have never seen a man who can jump out of bed, say his prayers, shave and dress as quickly as Dr. Hurd does, and he does not in any way curtail the length of his prayers."

BOOKS WRITTEN BY DR. HURD

HOSPITALS, DISPENSARIES AND NURSING

EDITED BY JOHN S. BILLINGS, M. D., AND HENRY M. HURD, M. D.

The International Congress of Charities, Correction and Philanthropy was held in Chicago, June 12 to 17, 1893. Section 3 was devoted to the hospital care of the sick, training of nurses, dispensary work and first aid to the injured. Dr. John S. Billings was chairman and Dr. Henry M. Hurd secretary of this section; Miss Isabel A. Hampton was chairman of the subsection on Nursing.

Many valuable papers were read in the section and it was clearly evident that the addresses should be published, but the necessary funds were lacking. Dr. Billings and Dr. Hurd came to the rescue and at their own expense published and also edited the large volume of over 700 pages. This splendid publication is of much interest to Baltimoreans not only on account of the many valuable papers, but also because Baltimoreans contributed in no small measure to the success of the Congress.

Dr. Billings' chairmanship address was entitled "The Relations of Hospitals to Public Health." Miss Hampton took for her theme "Educational Standards for Nurses," and Miss L. L. Dock spoke on "The Relation of Training Schools to Hospitals."

Dr. Hurd's address was on "The Relation of Hospitals to Medical Education." Mr. Henry C. Burdett, of London, England, the Honorary Chairman of the Section, in discussing Dr. Hurd's paper said:

I should like to say that I think it is very important that we should have a paper of this kind read this session. It is important because it clearly lays down and brings out clearly to the non-technical mind the reason why the cost of administering hospitals tends steadily to increase, and what those who give to hospitals really get back in return for their money. A man is often amazed by the demands which are constantly made for more and more money, especially for buildings, and I do

think that Dr. Hurd's paper will fulfill a very useful purpose, and I hope it will be printed and widely circulated among hospitals. . . .

Miss M. A. Boland, the dietitian of The Johns Hopkins Hospital, gave an interesting address on "Hospital Dietaries."

Dr. Hurd gave a second paper "Description of The Johns Hopkins Hospital." After briefly detailing the gift of Johns Hopkins and speaking of the plans and building of the hospital, he described the institution in detail, giving numerous illustrations and plans. The picture that will appeal most to the older members of the faculty is the one of the isolation ward, with the old boardwalk extending from the northern exit of this building over to the steps of the pathological building. One can even now vividly see those going from the hospital to the laboratory in rainy weather, turning up their coat collars and sprinting rapidly over to the pathological department.

The Congress was honored by a paper "Sick Nursing and Health Nursing" by Florence Nightingale, and by an address by our own Cardinal Gibbons on "Work Done by Religious Communities Devoted to the Relief of the Sick."

Too much credit cannot be given to Dr. Billings and to Dr. Hurd not only for editing, but also for bearing the cost of this volume which contains valuable articles from specialists in all parts of the world.

SUGGESTIONS TO HOSPITAL VISITORS

In 1895 Dr. John S. Billings and Dr. Hurd brought out a small book entitled "Suggestions to Hospital and Asylum Visitors." The need for such a book was very evident and S. Weir Mitchell prevailed upon these well-known hospital authorities to write it. Dr. Mitchell's introduction is so much to the point that I quote it in full:

For several years I have been urging upon Professor Billings the need for a small manual suited to the wants of hospital visitors. I have many times been asked by laymen who have to manage eleemosynary institutions where they could learn how critically to inspect them with a reasonable chance of seeing what is wrong and learning how to value what is praiseworthy. It is useless to point the inquirer to the greater works on hygiene. These presuppose such knowledge as few possess who are not educated physicians. There is needed a condensed statement of *what* to see in a hospital and *how* to see it.

Every new domain of observation requires a peculiar and individualized training. The acute microscopist might be a dull observer of the facts of disease which we call symptoms; the clever artist may be a sad failure when called upon to see with critical eyes the phenomena of the laboratory. How, then, can we expect that quite untrained people should of a sudden become useful observers in a field as new to them as is a hospital?

Boards of managers are chosen out of the every-day life of commerce and professions other than that of medicine. The members are presumed to study results into which enter questions of cooking, dietetics, ventilation, medical and surgical cleanliness, which involves disinfection, and many other matters exacting careful attention, and only to be thoroughly understood after years of training. This little manual is meant to assist untrained observers, yet even the most expert manager of a hospital or the ablest medical observer ought to find in it valuable hints. This guide to the hospital visitor I have asked leave to

introduce. It has cost an amount of care and thought out of proportion to its size. While in manuscript it was critically read by Professors J. M. DaCosta, J. William White, and myself, and certain changes or additions were suggested. Finally, Dr. Hurd, the accomplished director of The Johns Hopkins Hospital, was kind enough to associate himself with Professor Billings and to take the utmost interest in the work. Out of their joint labor and the criticism of able physicians and nurses has come at last the helpful little book which originated in my suggestion, and which I confidently commend to all who, being managers, trustees, or in any way connected with hospital work, are not contented to assume an official name and remain ignorant of how honestly to fulfill the duties which should go with it.

S. WEIR MITCHELL, M. D.

It is doubtful if any small book of 43 pages was ever so crammed full of information and good advice. It should be reprinted and be read by every hospital trustee and by all in any way interested in hospitals. A perusal of its pages will give the reader a very clear idea of the manifold details of hospital management, will enable him to render valuable advice without unjust criticism and will make the path of the superintendent or director of the hospital a much smoother one. In short, it will promote the maximum efficiency with friction reduced to the minimum.

The copy of the book that fell into my hands contains a few notes in Dr. Hurd's hand writing. These I venture to reproduce here without his knowledge or permission:

SUGGESTIONS FOR THE ORGANIZATION OF AUXILIARY BOARDS OF VISITORS

1. Composed of men and women who are interested in humanitarian and philanthropic work.
2. They should be absolutely free from any partisan or political bias.
3. They should feel at liberty to make suggestions as to the policy of the hospital, as to purchasing, administrative details, etc. They should be contented to present their views to the governing body with whom must rest the responsibility of the final decision.
4. They should seek to assist in all social service matters. The officers of a hospital, as a rule, are not widely acquainted with the possibilities of social help in the community or the sources of aid. The Board of Visitors can do incalculable good by bringing the hospital into relation with all helping agencies.
5. Boards of Visitors should never lose sight of the fact that they are privileged to assist in a most important public service. The increasing wealth of the country and the growth of a leisure class can only do harm if these become a source of personal pleasure to those who have leisure and abundant means. If, however, they use their good fortune for the public good, new aspirations are aroused and new and most satisfying channels of activity are found which dignify and ennoble the individual and bless the community. Personal service to hospitals and similar charities thus become not only a duty but a pleasure, and life is enlarged and made purposeful by the performance of good work.

THE INSTITUTIONAL CARE OF THE INSANE IN THE UNITED STATES AND CANADA

At the 66th annual meeting of the American Medico-Psychological Association held in Washington, D. C., in May, 1910, Dr. Hurd gave an address entitled "A History of Institutional Care of the Insane in the United States and Canada."

This paper was published in the *American Journal of Insanity*, 1910-11, Vol. lxvii, p. 587. In the course of his address Dr. Hurd said:

The movement to write a history of the association and its work had its origin at the Baltimore meeting in 1895, when Dr. Powell, of Georgia, presented a very interesting outline of the "rise and progress of a vast system of charities in the 15 commonwealths of the South," with detailed accounts of institutions in Virginia, North Carolina and Georgia. It was evident from the interest which was then excited that much had been done by similar foundations in all the states of the Union, and from this conviction grew the original resolutions subsequently presented by Dr. J. W. Babcock, of Columbia, S. C. These resolutions were considered and favorably acted upon, and a committee was appointed, but nothing seems to have come of it, although progress has been reported from time to time, and an effort has been made to stir up a general sentiment in favor of completing the work. For this and other reasons, although not aware of any special personal fitness for the work, I did not feel at liberty to decline the appointment made at the Cincinnati meeting, and of which, by the way, I learned for the first time in June last at Atlantic City. Since that time I have made an intermittent effort to organize the work and to collect such material as I could find.

The full committee consisted of Dr. Henry M. Hurd, chairman; Dr. William F. Drewry, for the South; Dr. Richard Dewey, for the West; Dr. Charles W. Pilgrim, for the middle states; Dr. G. Alder Blumer, for New England; Dr. T. J. W. Burgess, for British America.

The object of the present paper is to give some account of the progress of the work and to say what needs to be done. I hope, also, to stir up in the minds of the members of the association a feeling of responsibility for it, so that there may be coöperation in gathering the material and preparing it for publication at the proper time. The difficulties in the task are very great. Those who have been interested in the construction of the institutions for the insane in the United States have been largely isolated workers, and their records are, consequently, widely scattered throughout the different states of the Union. . . .

In his concluding paragraph Dr. Hurd says:

I have taken the liberty to embody the substance of this paper in a resolution which I now offer to ascertain the will of the association in the matter of the publication of the book. I shall be very glad to have it modified, revised, or in any way changed so as to bring out more completely the wishes of the association in this matter. I am not wedded to any theory of publication, or any form of work. I am anxious that the work go on with as much rapidity as possible. It is equally important, however, that the work be done thoroughly, so that in future all may know who in the past contributed to the success of an important philanthropic achievement.

Volumes I, II and III of this stupendous work appeared from The Johns Hopkins Press in 1916 and Volume IV in 1917. These four volumes contain in all 2926 pages.

A glance at the preface to Volume I gives the reader a clear idea of the tremendous amount of labor entailed in the preparation of these volumes. After taking up nearly three pages of the preface in thanking various men for their cordial coöperation in furnishing data the editor says:

The obligations of the committee to the individual superintendents of nearly 200 institutions in the United States and Canada are very great; in fact, without their coöperation it would

have been impracticable to prepare any adequate history of the movements in the various states and provinces.

It is evident from a careful study of all the material which has come into the hands of the committee that a gradual evolution has occurred in the care of the insane in America during the past half-century, which bids fair to change materially the discouraging views as to the hopelessness of their cure which have prevailed for many years in the United States and Canada.

The movement towards the prompt treatment of curable cases without the formality of legal commitment and under the same conditions as in admission to a hospital for general bodily disease, gives every hope that at an early day cases of recent attack may be received everywhere promptly, and that greatly increased numbers can be cured. Cases of a chronic nature are also now much more satisfactorily dealt with in institutions on the cottage plan, with out-lying colonies for the employment of patients, and have a correspondingly better opportunity to attain self-support. These movements promise to make material changes in future methods of caring for the insane.

Volume I is historical in character. It gives a clear account of the Association of Medical Superintendents of American Institutions for the Insane from 1844 to 1893 and of the American Medico-Psychological Association from 1893 to 1913. It then describes what the *American Journal of Insanity* has accomplished. Volume I was written by Dr. Hurd and the reader can best obtain an idea of the wide range of subjects considered in this volume by glancing through its lists of contents:

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Volumes II and III and part of Volume IV are devoted to a detailed description of the institutions for the care of the insane in the United States and Canada. Volume III also includes the institutions in Hawaii and in the Philippines. Pictures of many of the institutions are given and often plans of the buildings accompany them. In each article is a detailed list of the medical personnel of the institution from its beginning to the time the volume appeared, so that the previous activities of any man who has devoted his life to psychiatry can be readily followed.

The latter half of Volume IV is devoted to biographies of prominent psychiatrists in the United States and Canada.

The picture in Volume I that will interest Baltimoreans most is that of the Maryland Hospital for the Insane as it appeared in 1832. It faces on the old Joppa Road and in the background is the present Church Home and Infirmary, then the Washington Medical School. The site of the Old Maryland Hospital for the Insane is, as has been mentioned elsewhere, now occupied by The Johns Hopkins Hospital.

In Volume II is a splendid plate of the Sheppard and Enoch Pratt Hospital. The frontispiece of Volume IV is a reproduction of a portrait of Miss Dorothea L. Dix, to whose pioneer labors American psychiatry owes so much.

These volumes have brought forth much praise. *Science* for July 28, 1916, in reviewing Volume I, which was written in its entirety by Dr. Hurd, says:

This is one of the few works in the English language in which the history of a separate branch of medicine has been exhaustively treated. . . . The present volume, although it professes to deal only with the general history of institutional care of the insane on this continent, is, in reality, an exhaustive history of American psychiatry in all its phases, and is therefore likely to remain the authoritative work on the subject for an indefinite period. . . .

Dr. Hurd modestly regards this work as a source-book for the historians of the future but it is undoubtedly a permanent history which may be extended, but will hardly be duplicated. The chapters are complete in themselves, the book is well illustrated, and the style is charming in its simplicity, sobriety and its traces of delicate humor.

The *American Journal of Insanity* for October, 1916, in the course of the review of Volumes I and II, says:

Too much praise cannot be given to the manner in which the task imposed upon this Editorial Committee has been carried out, and as one of the members of the committee, Dr. Burgess, said at the meeting in New Orleans in April last, while all the committee have tried to help, the burden of the work has been on Dr. Hurd's shoulders.

The Nation on February 8, 1917, says:

No survey of the treatment of American insane during the last two centuries has before appeared; it is pleasant to find the difficult task so well executed as in this volume.

The British Medical Journal for December 8, 1917, in referring to the four volumes said:

Dr. Hurd is to be congratulated upon the success with which he has carried out the collection and colligation of the numerous interesting records contained in these volumes. Naturally they will appeal most strongly to readers across the Atlantic; but in their record and analysis of success and failure in attacking a problem of great importance in all civilized communities—namely, the care of the insane—they should find many readers throughout the world.

In another foreign review we find the following tribute:

This monumental work, is, in the main, the product of the veteran Dr. Hurd, emeritus professor of psychiatry in The Johns Hopkins University, and formerly medical superintendent of the Pontiac State Hospital, who is well known on this side of the Atlantic as the most distinguished of American alienists. Dr. Hurd has retired from active practice, but his abundant energy would not suffer him to be idle, and he has employed his leisure wisely and well in producing this great work, which will be a classic from the day of publication.

It must be remembered that during the immense amount of labor entailed in the preparation of these volumes Dr. Hurd had been greatly troubled with his eyes and it was only his indomitable will that continually spurred him on to the completion of these labors that were a fitting climax to his many successful years of hospital directorship.

SUMMARY *

Dr. Hurd in addition to his other editorial duties has been one of the editors of the *American Journal of Insanity* since 1897 and of the *Modern Hospital* since 1913.

He is a member of the Association of American Physicians; of the American Academy of Medicine, and was its president in 1896; of the American Medico-Psychological Association, of this he was secretary from 1892 to 1897 and president in 1898-9, he also edited three volumes of its proceedings; of the American Anthropological Association; of the American Hospital Association and its president in 1912. He is also a member of the American Public Health Association.

In 1895 Dr. Hurd was given the degree of LL. D. by his alma mater, the University of Michigan.

On September 16, 1874, Dr. Hurd married Miss Mary Doolittle, of Utica, N. Y. They had three children, a son and two daughters. The son died in childhood.

Mrs. Hurd was always greatly interested in her husband's labors and ever manifested the same cordial relation to the hospital interns and to the senior staff that Dr. Hurd did. A year or two after they left the hospital Mrs. Hurd's health began to fail and her death on March 14, 1913, was keenly felt by the host of friends of the family.

Miss Eleanor and Miss Anna Hurd are the constant companions of their father and it is a delight to see the manner in which they watch over his welfare and literally force him to conserve his unbounded energy.

Dr. Hurd is a Presbyterian. He has shown the same fidelity to his church that he has ever manifested in his professional duties.

From the preceding pages of this article the reader will see from what an intellectually sturdy stock he came and few men have had such a long medical ancestry. Step by step he rose until he was not only the first superintendent of a large asylum in Michigan, but also a dominant figure in that commonwealth. His fame as an administrator was not confined to his own locality, but was widely known. It was for this reason that he was later called to Baltimore.

All through his career he has been a thoroughly consistent and industrious psychiatrist. He has published many valuable papers dealing with the study and treatment of the insane, has for years been one of the editors of the *American Journal of Insanity* and less than three years ago edited a monumental work of four volumes on "The Institutional Care of the Insane

* This article together with "Random Recollections" by Dr. Hurd will be issued in book form from The Johns Hopkins Press in a few weeks.



HENRY M. HURD AND GEORGE KEEN MCGAW.

This is from a group picture that Dr. Hurd, Mr. McGaw and the author had taken in 1917.

in the United States and Canada." As mentioned before he wrote Volume I and edited Volumes II, III and IV.

For years he has been a most valuable member of the Maryland State Lunacy Commission. A foreign journal speaks of Dr. Hurd as "The most distinguished of American alienists." It is clearly evident that in psychiatry he has reached the top rung of the ladder.

The trustees of The Johns Hopkins Hospital manifested rare discernment when they selected Dr. Hurd to become the first superintendent of the hospital. It fairly blossomed under his wise generalship until its fame spread far beyond the confines of this continent—until it was known in every civilized land.

THE JOHNS HOPKINS HOSPITAL BULLETIN and the *Hospital Reports* under his able editorship added greatly to the prestige of the institution. As an expert in hospital organization and in hospital management he is recognized as the leader in America. His advice in hospital and nursing problems is continually sought. His is invariably the final word on these subjects.

His writings on hospital organization, hospital management, medical education and nursing are numerous and most valuable and he has ever aimed to publish historical records in order that they may not be lost—in order that they may be preserved for future generations. Whatever he has undertaken he has finished.

A prominent publisher who has come in contact with him nearly every week for at least 25 years said to me recently "Dr. Hurd is the most practical and business-like physician that I have ever met"—and he meets an unusually large number. It is undoubtedly this practical bent, coupled with rare discernment, a broad knowledge of men and a wide knowledge of psychiatry and medicine that has enabled him to accomplish so much apparently with so little effort.

From time to time brilliant statesmen advanced in years have been spoken of as "grand old men." Dr. Hurd is the grand old hospital statesman of America. Early in his career he wanted to become a surgeon in the navy, but was disqualified on account of his frail physical make-up. He would have undoubtedly made his mark in government service, but what a loss the asylums and hospitals of this country would have sustained, and how much psychiatry and the profession of medicine in general would have missed had he successfully passed the physical requirements for the navy!

His has been a life well spent—a life full of labor for his fellow man. In a memorial tribute to the late Dr. William Whitney Godding, Dr. Hurd unconsciously gave a most vivid description of himself. "You felt instinctively that you had to do with one who knew no guile or self-seeking, but who appreciated it to be his duty to place his powers of mind and heart unreservedly at the disposal of his associates or his fellow men." But Dr. Hurd is not gone, he is still with us, actively engaged in writing the history of The Johns Hopkins Hospital. That he may long be spared to browse in the Henry M. Hurd Library, which my friend George K. McGaw is building as a mark of appreciation and esteem to our mutual

friend, the first superintendent of The Johns Hopkins Hospital, is our earnest prayer.

THE LATE GEORGE KEEN MCGAW

For several months Mr. McGaw had been failing in health, and in June he went to his summer home at Buena Vista. The erection of the Henry M. Hurd library was uppermost in his mind, and the last thing he did on the morning he left for the mountains was to turn over to Judge Harlan additional funds for the building. He was particularly anxious that Dr. Hurd should not only see, but also have the opportunity of often enjoying the library bearing his name. My account of Dr. Hurd's manifold activities was accordingly promptly undertaken and as soon as it was completed, early in July, Judge Harlan and I spent a delightful day with Mr. McGaw and his family in the mountains. For fully two hours Mr. McGaw listened with great interest to the recital of the many things his friend had accomplished and again expressed himself as so happy that the library plans were well under way. That was the last time I saw that whole-souled and true friend. He had a fairly comfortable summer. He died suddenly on the morning of September 9, 1919.

Dr. Hurd and Mr. McGaw had known one another for many years, as they both were prominent members of the First Presbyterian Church and Mr. McGaw was also one of the Trustees of The Johns Hopkins Hospital.

In March, 1911, Mr. McGaw suggested a trip South and a few days later Dr. Hurd, Mr. McGaw and myself left for an extended trip, visiting Pinehurst, Columbia, Savannah, Jacksonville, Knights Key, Havana, Key West and Miami. It was on this trip that the lasting and intimate companionship and friendship was cemented between these two splendid men, and since that time they have been together week in and week out. It was this close companionship that revealed to Mr. McGaw Dr. Hurd's wonderful breadth of character, and that prompted him to plan this tribute to his friend—a tribute that will not only be a constant reminder of the first superintendent of The Johns Hopkins Hospital, but that will also be of inestimable value to the succeeding generations of students in The Johns Hopkins Medical School.

Dr. Hurd's estimate of his departed friend rings so true and is so beautifully expressed in a recent letter to me that I cannot help reproducing it here.

SEAL HARBOR, ME., Sept. 13, 1919.

DEAR CULLEN: Many thanks for your telegrams and your thoughtfulness in sending them. I have been greatly shocked by the unexpected death of the best of friends and I know of no one who may occupy the vacant place in just the same way. He was so noble in his plans and modest in carrying them out, so that his own work might be minimized. I always felt him to be a rare man. We all of us ought to be better men for having known him. I have written to Mrs. McGaw, but I feel that I could not in any way tell her properly how much I loved him. . . .

Sincerely,

HENRY M. HURD.

BIBLIOGRAPHY OF HENRY MILLS HURD, M. D., LL. D.

PREPARED BY

MINNIE WRIGHT BLOGG

LIBRARIAN, THE JOHNS HOPKINS HOSPITAL

1881

Recent judicial decisions in Michigan relative to insanity. *Am. J. Insan., Utica, N. Y., 1880-81, xxxvii, 23-35.*

1882

A plea for systematic therapeutical, clinical and statistical study. Read before the Association of Medical Superintendents of American Institutions for the Insane, at the annual meeting in Toronto, June, 1881. *Am. J. Insan., Utica, N. Y., 1881-82, xxxviii, 16-31.*

Practical suggestions relative to the treatment of insanity. *Physician & Surg., Ann Arbor, Mich., 1882, iv, 385-399.*

1883

Future provision for the insane in Michigan. n. p., 1883. 9 p. 8°.

The treatment of periodic insanity. *Am. J. Insan., Utica, N. Y., 1882-83, xxxix, 174-180.*

Ducking in asylums. A refutation (letter). *Am. J. Insan., Utica, N. Y., 1882-83, xxxix, 506-507.*

The hereditary influence of alcoholic indulgence upon the production of insanity. A paper read at a sanitary convention held at Pontiac, Michigan, January 31 and February 1, 1883. Reprinted from a Supplement to the Annual Report of the Secretary of the State Board of Health of Michigan, for the year 1883. *Physician & Surg., Ann Arbor, Mich., 1883, v, 49-57.*

1884

The minor treatment of insane patients; summary. *Am. J. Insan., Utica, N. Y., 1883-84, xl, 205-209.*

1886

Paranoia. *Am. J. Insan., Utica, N. Y., 1885-86, xlii, 473-483.*

1887

The relation of general paresis and syphilitic insanity. *Am. J. Insan., Utica, N. Y., 1886-87, xliii, 1-18.*

The data of recovery from insanity. *Am. J. Insan., Utica, N. Y., 1886-87, xliii, 243-255.*

The colony system of Michigan. *Proc. Nat. Confer. Char., Bost., 1887, xiv, 215-220.*

1888

Gastric, secretory and other crises in general paresis. *Am. J. Insan., Utica, N. Y., 1887-88, xliv, 60-65.*

The religious delusions of the insane. *Am. J. Insan., Utica, N. Y., 1887-88, xliv, 471-487.*

Also: Tr. IX. Internat. M. Cong., Wash., 1887, v, 253-263.

Hurd, H. M. & Christian, E. A. The ultimate results in a case of exsection of the head and upper third of the humerus. *Ann. Surg., St. Louis, 1888, vii, 431-434.*

1889

Imbecility with insanity. *Am. J. Insan., Utica, N. Y., 1888-89, xlv, 261-269.*

1890

First report of the superintendent of The Johns Hopkins Hospital from May 15, 1889, to January 31, 1890. *Balt., 1890, The Johns Hopkins Press. 47 p. 8°.*

Also: Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 77-89.

A case of inebriety with insanity; with remarks. *Am. J. Insan., Utica, N. Y., 1889-90, xlv, 61-70.*

The relation of the Training School for Nurses to The Johns Hopkins Hospital. *Johns Hopkins Hosp. Bull., Balt., 1889-90, i, 7-8.*

Periodicity in melancholia. *Maryland M. J., Balt., 1890, xxiii, 269-270.*

Report of committee on hospitals. *Proc. Nat. Confer. Char., Bost., 1890, xvii, 155-156.*

The relation of the general hospital to the medical profession. *Proc. Nat. Confer. Char., Bost., 1890, xvii, 156-162.*

1891

Second report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1891. *Balt., 1891, The Johns Hopkins Press. 76 p. 8°.*

Also: Johns Hopkins Hosp. Bull., Balt., 1891, ii, 124-132.

Memoir of Richard Gundry, M. D. *Tr. M. & Chir. Fac. Maryland, Balt., 1891, 178-183.*

1892

Third report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1892. *Balt., The Johns Hopkins Press. 63 p. 8°.*

Also: Johns Hopkins Hosp. Bull., Balt., 1892, iii, 97-102.

Journal clubs. *Am. J. Insan., Utica, N. Y., 1891-92, xlviii, 372-375.*

Post-febrile insanity. *Maryland M. J., Balt., 1892, xxvii, 661-666.*

Also: Am. J. Insan., Utica, N. Y., 1892-93, xlix, 26-34.

1893

Fourth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1893. *Balt., 1893. The Johns Hopkins Press. 69 p. 8°.*

The relation of hospitals to medical education. *Boston M. & S. J., 1893, cxxix, 141-143.*

1894

Fifth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1894. *Balt., 1894. The Johns Hopkins Press. 69 p. 8°.*

Hurd, H. M. & Billings, J. S. *eds.* Hospitals, dispensaries and nursing. Papers and discussions in the International Congress of Charities, Correction and Philanthropy, section iii, Chicago, June 12-17, 1893. *Balt., 1894, Johns Hopkins Press. 733 p. 8°.*

The relation of hospitals to medical education.

In: Hospitals, Dispensaries and Nursing. . . Internat. Cong. Char. [etc.], 1893, Balt. & Lond., 1894, 98-105.

Description of the Johns Hopkins Hospital, Baltimore, Md.

In: Hospitals, Dispensaries and Nursing. . . Internat. Cong. Char. [etc.], 1893, Balt. & Lond., 1894, 429-443.

George Huntington Williams. The minutes of a commemorative meeting held in the Johns Hopkins University, October 14, 1894. *Baltimore, 13 p. 8°.*

Some mental disorders of childhood and youth. *Boston M. & S. J., 1894, cxxxi, 281-285.*

Also: Baltimore, 1895, Friedenwald Co., 16 p. 8°.

1895

Sixth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1895. *Balt., 1895. The Johns Hopkins Press. 74 p. 8°.*

Hurd, H. M. & Billings, J. S. Suggestions to hospital and asylum visitors. With an introduction by S. Weir Mitchell. *Phila., 1895, J. B. Lippincott Co., 48 p., 8°.*

The alienists of the past half century. *Proc. Am. Med. Psychol. Ass., 1894, Utica, N. Y., 1895, i, 167-171.*

1896

Seventh report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1896. *Balt., 1896. The Johns Hopkins Press. 66 p. 8°.*

The new McLean Hospital. *Am. J. Insan.*, Chicago, 1895-6, lii, 477-502.

Laboratories and hospital work. *Bull. Am. Acad. M.*, Easton, Pa., 1895-6, ii, 483-495.

Paranoia. Maryland M. J., Balt., 1896, xxxv, 1-4.

Also: [Abst.] Virginia M. Semi-Month., Richmond, 1896-7, i, 263.

1897

Eighth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1897. Balt., 1897. The Johns Hopkins Press. 88 p. 8°.

Hospital organization and management. Address before the Training School for Nurses of the University of Pennsylvania, February 17, 1897. *Univ. M. Mag.*, Phila., 1896-7, ix, 488-500.

Hurd, H. M., Burr, C. B. & Wise, P. M. Report of the committee on statistical tables, to the American Medico-Psychological Association. *Am. J. Insan.*, Chicago, 1896-7, liii, 105-116.

Hurd, H. M. & Chapin, J. B. Report on the hospitals of the District of Columbia. To the Joint Select Committee to investigate the charities and reformatory institutions in the District of Columbia, Washington, 1897.

1898

Ninth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1898. Balt., 1898. The Johns Hopkins Press. 91 p. 8°.

The medical service of hospitals. Albany M. Ann., 1898, xix, 137-142.

The non-medical treatment of epilepsy. (Proc. Johns Hopkins Hosp. Med. Soc., November 7, 1898). Johns Hopkins Hosp. Bull., Balt., 1898, ix, 296-297.

Also: Maryland M. J., Balt., 1898-9, xl, 53.

1899

Tenth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1899. Balt., 1899. The Johns Hopkins Press. 92 p. 8°.

Post-operative insanities and undetected tendencies to mental disease. *Am. J. Obst.*, N. Y., 1899, xxxix, 331-335.

Presidential address. The teaching of psychiatry. Delivered at the annual meeting of the American Medico-Psychological Association at New York, May 23, 1899. *Proc. Am. Med. Psychol. Ass.*, 1899, vi, 79-92.

Also: Johns Hopkins Hosp. Bull., Balt., 1899, x, 205-209.

Also: *Am. J. Insan.*, Balt., 1899-1900, lvi, 217-230.

1900

Eleventh report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1900. Balt., 1900. The Johns Hopkins Press. 114 p. 8°.

Memorial addresses in honor of William Whitney Godding, M. D., LL. D. Delivered before the Medical Society of the District of Columbia, June 7, 1899. *Nat. M. Rev.*, Wash., 1899-1900, ix, 374-377.

Hospitals, dispensaries and nursing. (American philanthropy of the nineteenth century). *Char. Rev.*, N. Y., 1900, x, 298-305; 317-331.

Hospital construction from a medical standpoint. Brickbuilder, Bost., 1900, ix, 248.

1901

Twelfth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1901. Balt., 1901. The Johns Hopkins Press. 114 p. 8°.

Reception hospitals for cases of acute insanity. *Bull. Iowa Inst.*, Des Moines, 1901, iii, 38-40.

1902

Thirteenth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1902. Balt., 1902. The Johns Hopkins Press. 118 p. 8°.

The educated nurse and her future work. Address delivered at the graduating exercises of the Training School of the Garfield Hospital, Washington, D. C.; and similarly at the Training School of the Methodist Episcopal Hospital, Brooklyn, N. Y. Baltimore [1902], Friedenwald Co., 14 p. 8°.

Psychiatry in the twentieth century. Address at the formal opening of the new hospital building at Morris Plains, New Jersey, November 20, 1901. Albany M. Ann., 1902, xxiii, 125-136.

1903

Fourteenth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1903. Balt., 1903. The Johns Hopkins Press. 110 p. 8°.

The future policy of Maryland in the care of her insane. Maryland M. J., Balt., 1903, xlvii, 45-54.

The duty and responsibility of the University in medical education. Science, N. Y. & Lancaster, Pa., 1903, n. s., xviii, 65-76.

Also: Yale M. J., 1903-4, x, 1-17.

1904

Fifteenth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1904. Balt., 1904. The Johns Hopkins Press. 130 p. 8°.

Is nursing a profession? Albany M. Ann., 1904, xxv, 625-637.

1905

Sixteenth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1905. Balt., 1905. The Johns Hopkins Press. 133 p. 8°.

John Howard's observations on hospitals (1773-1790). (Proc. Johns Hopkins Hosp. Med. Soc., October 23, 1905). Johns Hopkins Hosp. Bull., Balt., 1905, xvi, 412-413.

Also: Tr. Ass. Hosp. Superintend., 1905, vii, 157-166.

Response to Dr. Cheever's "Address of welcome." Tr. Ass. Hosp. Superintend., 1905, vii, 50-52.

1906

Seventeenth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1906. Balt., 1906. The Johns Hopkins Press. 125 p. 8°.

Shall training schools for nurses be endowed? An address delivered before the Training School for Nurses of Lakeside Hospital, Cleveland, May 11, 1906. *Am. J. Nursing*, Phila., 1905-6, vi, 843-853.

Also: Nat. Hosp. Rec., Detroit, 1906, x, 18-23.

Also: Brit. J. Nursing [etc.], Lond., 1906, xxxvii, 225-227.

The medical organization of general hospitals. Tr. Am. Hosp. Ass., 1906, viii, 72-83.

Also: Nat. Hosp. Rec., Detroit, 1906, x, 14-16.

1908

Nineteenth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1908. The Johns Hopkins Press. 123 p. 8°.

The proper length of the period of training for nurses. *Am. J. Nursing*, Phila., 1908, viii, 671-683.

How can psychiatry assist preventive medicine? (Editorial). *Am. J. Pub. Hyg.*, Boston, 1908, xviii, 273-278.

Psychiatry as a part of preventive medicine. *Proc. Am. Med. Psychol. Ass.*, Balt., 1908, xv, 157-164.

Also: *Am. J. Insan.*, Balt., 1908-9, lxxv, 17-24.

Also: N. Albany M. Herald, 1910, xxviii, 104-108.

In memoriam, Daniel Colt Gilman, 1831-1908. Address. Johns Hopkins Univ. Circ., Balt., 1908, xxvii, 20-23.

1909

Twentieth report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1909. Balt., 1909. The Johns Hopkins Press. 123 p. 8°.

State registration and the education of nurses in the United States. *Nursing Mirror*, Lond., 1908-9, n. s., viii, 37-38; 53.

In memoriam, William Keith Brooks, 1848-1908. Address. Johns Hopkins Univ. Circ., Balt., 1909, xxviii, 6-9.

1910

Twenty-first report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1910. Balt., 1910. The Johns Hopkins Press. 123 p. 8°.

Co-operation among hospitals. A paper presented to the Pittsburgh Health Conference, November 30, 1910, as a part of a symposium on "Co-operation."

Memorial services for Isabel Hampton Robb, who died April 15, 1910, at Cleveland, Ohio. Remarks. Johns Hopkins Hosp. Bull., Balt., 1910, xxi, 251-252.

Florence Nightingale—a force in medicine. Address at the graduating exercises of the Nurses Training School of the Johns Hopkins Hospital, May 19, 1910. Johns Hopkins Nurses Alumnae Mag., Balt., 1910, ix, 68-81.

1911

Twenty-second report of the superintendent of The Johns Hopkins Hospital for the year ending January 31, 1911. Balt., 1911. The Johns Hopkins Press. 109 p. 8°.

The medical service of a hospital. *In*: Hospital management, a handbook for hospital trustees, superintendents [etc.] (Aikens), Phila. & Lond., 1911, 97-107.

A history of institutional care of the insane in the United States and Canada. Am. J. Insan., Balt., 1910-11, lxvii, 587-592.
Also: Proc. Am. Med.-Psychol. Ass., Balt., 1910, xvii, 483-488.

The site of the Johns Hopkins Hospital. A paper presented to the Johns Hopkins Historical Club and repeated to the Teresians in December, 1910. Johns Hopkins Nurses Alumnae Mag., Balt., 1911, x, 5-20.

The proper relation of the superintendent to the trustees of a hospital. Tr. Am. Hosp. Ass., 1910, Toronto, 1911, xii, 244-248.

1912

The proper division of the services of the hospital. Read in the symposium on the relations of the hospital to the public in the section on hospitals of the American Medical Association, at the sixty-third annual session, held at Atlantic City, June, 1912. J. Am. M. Ass., Chicago, 1912, lix, 1677-1679.

[Hospital problems.] Presidential address at the fourteenth annual conference of the American Hospital Association. Internat. Hosp. Rec., Detroit, 1912, xvi, 9-11.
Also: Tr. Ass. Hosp. Superintend., 1912, xiv, 83-93.

Meeting in behalf of the Isabel Hampton Robb Memorial Fund. Remarks. Johns Hopkins Nurses Alumnae Mag., Balt., 1912, xi, 16-19.

1913

Three-quarters of a century of institutional care of the insane in the United States. Am. J. Insan., Balt., 1912-13, lxix, 469-481.

Extracts from the laws of Maryland and Virginia regarding the early care of the insane. Bull. Med. & Chir. Fac. Maryland, Balt., 1912-13, v, 85-88.

Early days of The Johns Hopkins Hospital and Medical School. Johns Hopkins Alumni Mag., Balt., 1912-13, i, 105-114.

The hospital as a factor in modern society. (Editorial). Mod. Hosp., St. Louis, 1913, i, 33.

Hospitals and the reform of medical teaching. (Editorial). Mod. Hosp., St. Louis, 1913, i, 182-183.

Review of "A History of Nursing." Johns Hopkins Nurses Alumnae Mag., Balt., 1913, xii, 91-94.

1914

Hospital medical statistics. (Editorial). Mod. Hosp., St. Louis, 1914, ii, 44-45.

The small hospital a factor in medical education. (Editorial). Mod. Hosp., St. Louis, 1914, ii, 104-105.

Mental cases in general hospitals. (Editorial). Mod. Hosp., St. Louis, 1914, ii, 172.

The human side of Florence Nightingale. (Editorial). Mod. Hosp., St. Louis, 1914, ii, 364.

State registration of nurses. Mod. Hosp., St. Louis, 1914, iii, 107; 137.

Dr. Rupert Norton. (Editorial). Mod. Hosp., St. Louis, 1914, iii, 108-109.

Some of the writings of the late Eugene Fauntleroy Cordell. Bull. Med. & Chir. Fac. Maryland, Balt., 1913-14, vi, 115-119.

Relation of the general hospital to the training school for nurses. Boston M. & S. J., 1914, clxx, 333-337.

Twenty-fifth anniversary of The Johns Hopkins Hospital. 1889-1914. Address. Johns Hopkins Hosp. Bull., Balt., 1914, xxv, 355-359.

Presentation of tablets, portrait and medallion at the Hospital October 7, 1914. Remarks. Johns Hopkins Hospital Bull., Balt., 1914, xxv, 368-369.

Hurd, H. M., McCaw, W. D. [et al.] Johns Hopkins Historical Club. Special meeting, May 26, 1913, in memory of Dr. John Shaw Billings. Johns Hopkins Hosp. Bull., Balt., 1914, xxv, 244-253.

1915

Hospital organization and management. Ref. Handb. Med. Sc., N. Y., 3d ed., 1915, v, 299-311.

The treatment of mental cases in general hospitals. (Editorial). Mod. Hosp., St. Louis, 1915, iv, 34-35.

The general government of state hospitals. Mod. Hosp., St. Louis, 1915, iv, 244-245.

Organization and administration of hospitals for the insane. (Editorial). Mod. Hosp., St. Louis, 1915, iv, 258.

Ought training schools for nurses to be endowed? (Editorial). Johns Hopkins Nurses Alumnae Mag., Balt., 1915, xiv, 2-3.

The early years of The Johns Hopkins Hospital. Johns Hopkins Nurses Alumnae Mag., Balt., 1915, xiv, 76-89.

Forty-five years ago and now. An address before the Training School for Nurses at the Sheppard and Enoch Pratt Hospital, May 19, 1915. Johns Hopkins Nurses Alumnae Mag., Balt., 1915, xiv, 256-264.

The care of cases of mental disease in general hospitals. Tr. Am. Hosp. Ass., 1915, xvii, 455-462.

Also: Mod. Hosp., St. Louis, 1915, v, 33-35.

1916

Hurd, H. M., Drewry, W. F. [et al.] The institutional care of the insane in the United States and Canada. 3 v., Balt., 1916, Johns Hopkins Press. 8°.

Nathan Smith, Nathan R. Smith, and Alan P. Smith—a medical family. Maryland M. J., Balt., 1916, lix, 56-59.
Also: Bull. Med. & Chir. Fac. Maryland, Balt., 1915-16, viii, 157-163.

Address on the occasion of the opening of the John Hubner Psychopathic Building at Springfield State Hospital, on June 9, 1915. Maryland Psychiat. Q., Balt., 1915-16, v, 29-32.

Need of segregation of imbecile women. Maryland Psychiat. Q., Balt., 1915-16, v, 64-67.

Report of committee on a history of "The Institutional Care of the Insane in the United States and Canada." Am. J. Insan., Utica, N. Y., 1915-16, lxxii, 176-177.

Some sources of friction in the management of hospitals. (Editorial). Mod. Hosp., St. Louis, 1916, vi, 30-31.

Another source of friction in hospital administration. (Editorial). Mod. Hosp., St. Louis, 1916, vi, 112.

Who shall manage the training school for nurses? Mod. Hosp., St. Louis, 1916, vi, 114-115.

Advantages of the budget system. (Editorial). Mod. Hosp., St. Louis, 1916, vi, 186.

1917

Hurd, H. M., Drewry, W. F. [et al.] The institutional care of the insane in the United States and Canada. Vol. iv, Balt., 1917, Johns Hopkins Press. 652 p., 8°.

Johns Hopkins and some of his contemporaries. Johns Hopkins Hosp. Bull., Balt., 1917, xxviii, 225-229.

State hospitals and agricultural preparedness. (Editorial). Mod. Hosp., St. Louis, 1917, ix, 24.

Burket, W. C. Bibliography of William H. Welch, M. D., LL. D. With foreword by Henry M. Hurd. Balt., 1917, Johns Hopkins Press. 47 p., 4°.

1919

A sketch of Dr. Lyman Spalding. Johns Hopkins Hosp. Bull., Balt., 1919, xxx, 125-129.

Also: Bull. Med. Library Ass., Balt., 1918-19, viii, 29-38.

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